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CONTENTS OF VOLUME 38

CONTENTS OF VOLUME 38

FEBRUARY—Continued

MARCH 1939. NUMBER 3

CONTENTS OF VOLUME 38

APRIL 1939. NUMBER 4

MAY 1939. NUMBER 5

MAY—*Continued*

JUNE 1939. NUMBER 6

SURGICAL IMPORTANCE OF MAMMARY AND SUBCUTANEOUS FAT NECROSIS

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A thorough knowledge of the pathogenesis and clinical manifestations of fat necrosis is of considerable surgical importance because all too frequently the similarity of this condition to cancer has led to ill advised surgical intervention or irradiation therapy. This is particularly true of fat necrosis in the breast, despite the accurate description of this condition as a clinical entity over a decade ago.[1] However, fat necrosis may prove to be equally baffling or even more so when it occurs in a mastectomy scar, in a lipoma, in a hernial sac or deep in the subcutaneous tissues of the thigh or the buttock. It is the purpose of the present paper to call attention once again to the inherent difficulties in recognizing this condition and to emphasize its importance in the differential diagnosis of malignant lesions in the breast or of the superficial tissues.

One of the earliest descriptions of extra-abdominal fat necrosis was that of Shattock, who in 1896 described an occurrence of "saponifying necrosis" in a lipoma of the thigh. Since that time the condition has been described under a number of titles, of which the most familiar are "traumatic fat necrosis," [1] "ischaemic fat necrosis" [2] and "lipogranulomatosis." [3] Since fat necrosis is not a true granuloma and since it may occur independently of proved trauma or ischemia, it seems better to designate it according to its anatomic location as "mammary" or "subcutaneous" fat necrosis.

Usually fat necrosis appears as a solitary lesion, but its lesions may be multiple, especially in the newborn. In such patients it must be distinguished from sclerema and scleroderma neonatorum. It is a well

From the Surgical and Pathologic Services of the Peter Bent Brigham Hospital.

1. Lee, B. J., and Adair, F.: Traumatic Fat Necrosis of the Female Breast and Its Differentiation from Carcinoma, Ann. Surg. **72**:188 (Aug.) 1920.

2. Farr, C. E.: Ischaemic Fat Necrosis, Ann. Surg. **77**:513-523 (May) 1923.

3. Harbitz, H. F.: Lipogranuloma—Foreign Body Inflammation Often Suggesting Tumor, Acta chir. Scandinav. **76**:401-426, 1935.

defined entity; it is almost certainly the result of trauma; and in contradistinction to scleroderma neonatorum it has a uniformly good prognosis.[4] In the adult, multiple areas of fat necrosis are of rare occurrence, but they have been described as following infectious diseases.[5] It is possible that such multiple areas of fat necrosis are the result of ischemia due to vascular lesions. Christian-Weber's disease is included in this classification by some authorities.

It is with the solitary lesions of fat necrosis, however, that the surgeon is particularly concerned. The exact factors involved in the development of this condition have not been established. The lesion may arise after trauma, after the injection of foreign material, especially fats and oils, after interference with the blood supply to a part or after infection. However, if any of these factors alone is sufficient to produce fat necrosis it is difficult to understand the comparative rarity of the lesion when one considers the frequency of trauma to, and infection in, subcutaneous fat. It seems likely, therefore, that in addition to these various exogenous factors an endogenous factor is essential for the production of fat necrosis. The nature of this endogenous factor is hypothetic, but it may be a blood or tissue lipase [6] which is more abundant or more easily activated in certain persons than in others.

In evaluating the experimental production of fat necrosis as well as in diagnosing the condition of pathologic material it is well to bear in mind that fat splitting and fat necrosis may be separate processes which, although usually closely allied, are not necessarily so.[2] Thus, the presence of fat crystals alone is not sufficient histologic evidence to warrant a diagnosis of fat necrosis. Also, after the injection of foreign material, especially fats and oils, an intense foreign body reaction may be observed; such a reaction is not necessarily fat necrosis. In certain cases this foreign body reaction becomes a progressive lesion which possesses the essential histologic features of fat necrosis. That this is not always the case, however, can be seen in figure 1, which represents the reaction produced by injection of cod liver oil into the peritoneal fat of a guinea pig. It should be noted that although there is a marked foreign body reaction the adjacent fat appears normal. It should be noted also that there is no actual necrosis of fat with the formation of confluent polyhedral spaces much larger than a normal fat cell, such as is seen in figure 2. This dissolution of normal fat cells into confluent

4. Fox, H.: Subcutaneous Fat Necrosis of the New-Born: Report of Five Cases, Arch. Dermat. & Syph. **27**:237-252 (Feb.) 1933.

5. Abrikossoff, A.: Ueber die spontan auftretende Fettgewebsnekrose und Fettgranulome, Centralbl. f. allg. Path. u. path. Anat. **38**:542-546 (Nov. 15) 1926; cited by Harbitz.[3]

6. Neal, M. P., and Ellis, M. M.: Etiological Factor of Fat Necrosis, South. M. J. **23**:313-320 (April) 1930; Experimental Fat Necrosis in Various Vertebrates, Am. J. Clin. Path. **1**:251-263 (May) 1931.

spaces seems to be an essential characteristic of true fat necrosis. It apparently represents one of the earliest histologic changes. Within these spaces are the products of the decomposing fat, which usually excite a mild but slowly progressive foreign body reaction. This is characterized chiefly by an infiltration of mononuclear phagocytes,

Fig. 1.—Photomicrograph ($\times$ 165) of the peritoneal fat of the guinea pig ten weeks after the injection of cod liver oil. Note the intense foreign body reaction without the formation of confluent spaces or vacuolated areas in the adjacent fat. Compare with figure 2. (The specimen was stained with eosin and methylene blue.)

many of which become filled with particles of necrotic fat. These so-called "foam cells" are found about the periphery of the broken-down fat (fig. 3). This is followed by proliferation of the surrounding
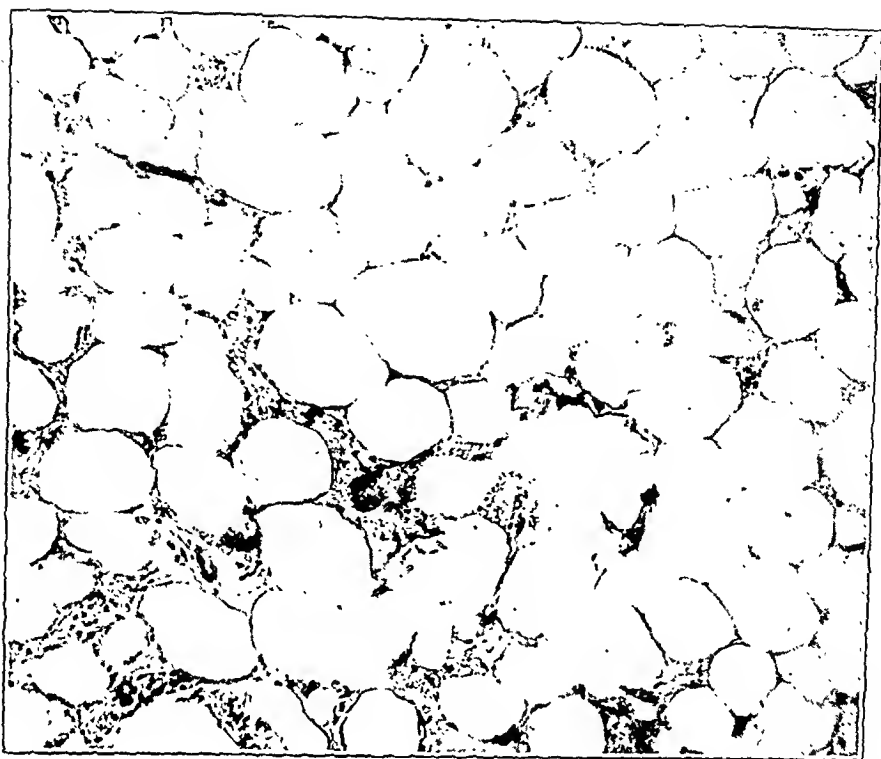
Fig. 2.—Photomicrograph (×90) showing the early changes of fat necrosis. In contrast to figure 1, in this tissue one finds irregular polyhedral spaces much larger than a normal fat cell. The formation of these confluent cystlike areas seems to be an essential histologic characteristic of fat necrosis. (The specimen was stained with eosin and methylene blue.)
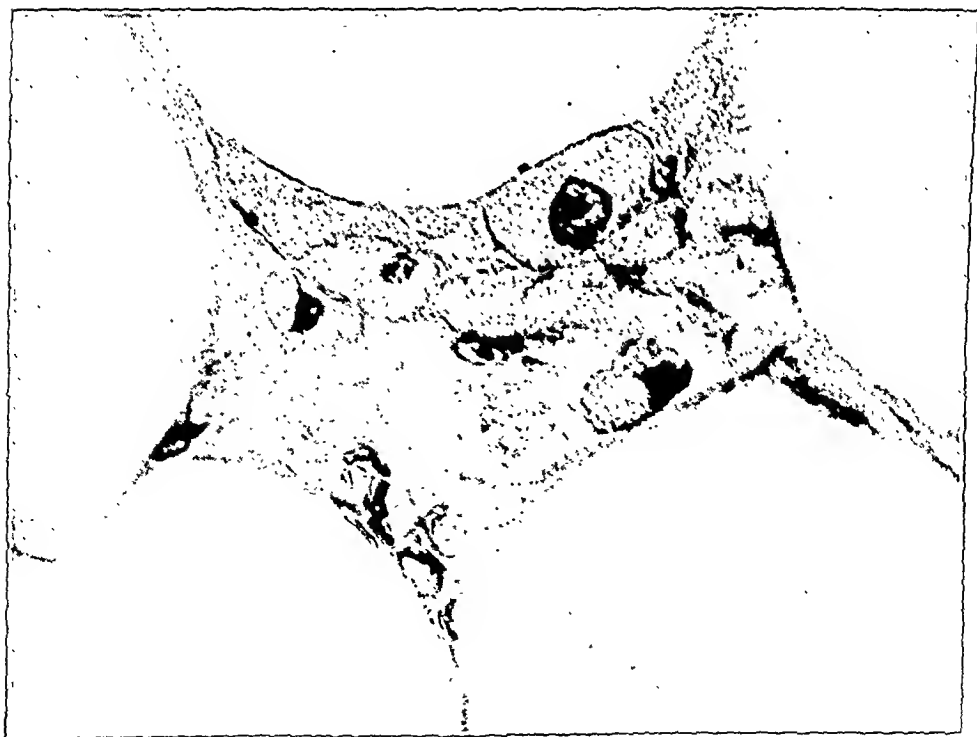
Fig. 3.—Photomicrograph (×900) showing the cellular reaction in early fat necrosis. The large mononuclear phagocytes are filled with the products of the decomposing fat, constituting the so-called "foam cells." (The specimen was stained with eosin and methylene blue.)
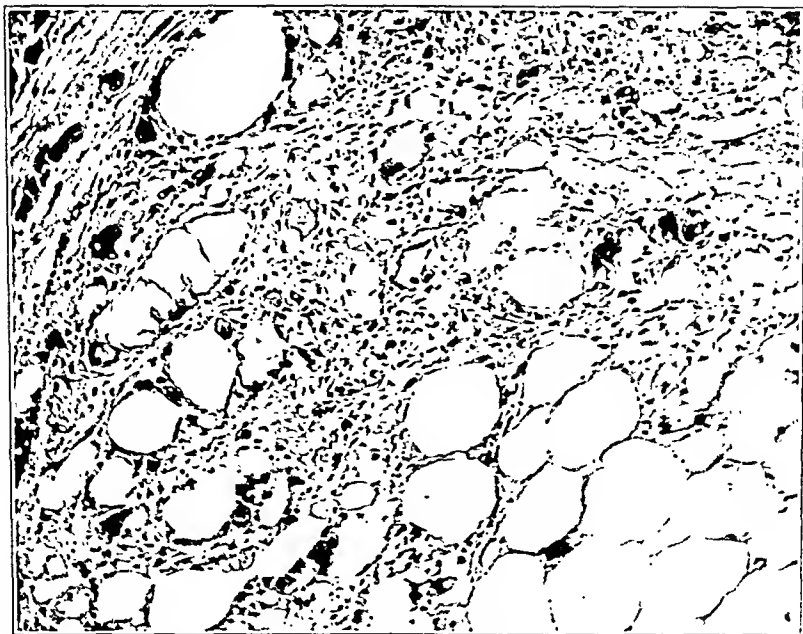
Fig. 4.—Photomicrograph ($\times 165$) of moderately advanced fat necrosis. Note the connective tissue proliferation about the broken-down confluent fat. (The specimen was stained with eosin and methylene blue.)
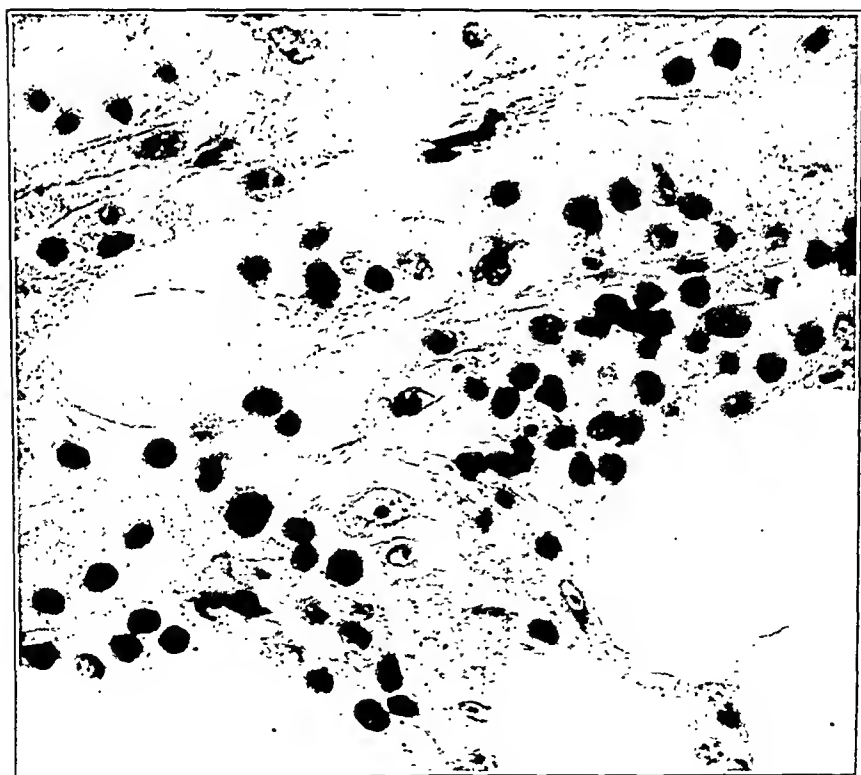
Fig. 5.—Photomicrograph ($\times 900$) showing the more abundant cellular reactions which may occur in fat necrosis. Here, in addition to mononuclear phagocytes, are numerous lymphocytes and plasma cells. In an earlier stage polymorphonuclear leukocytes may be seen. (The specimen was stained with eosin and methylene blue.)
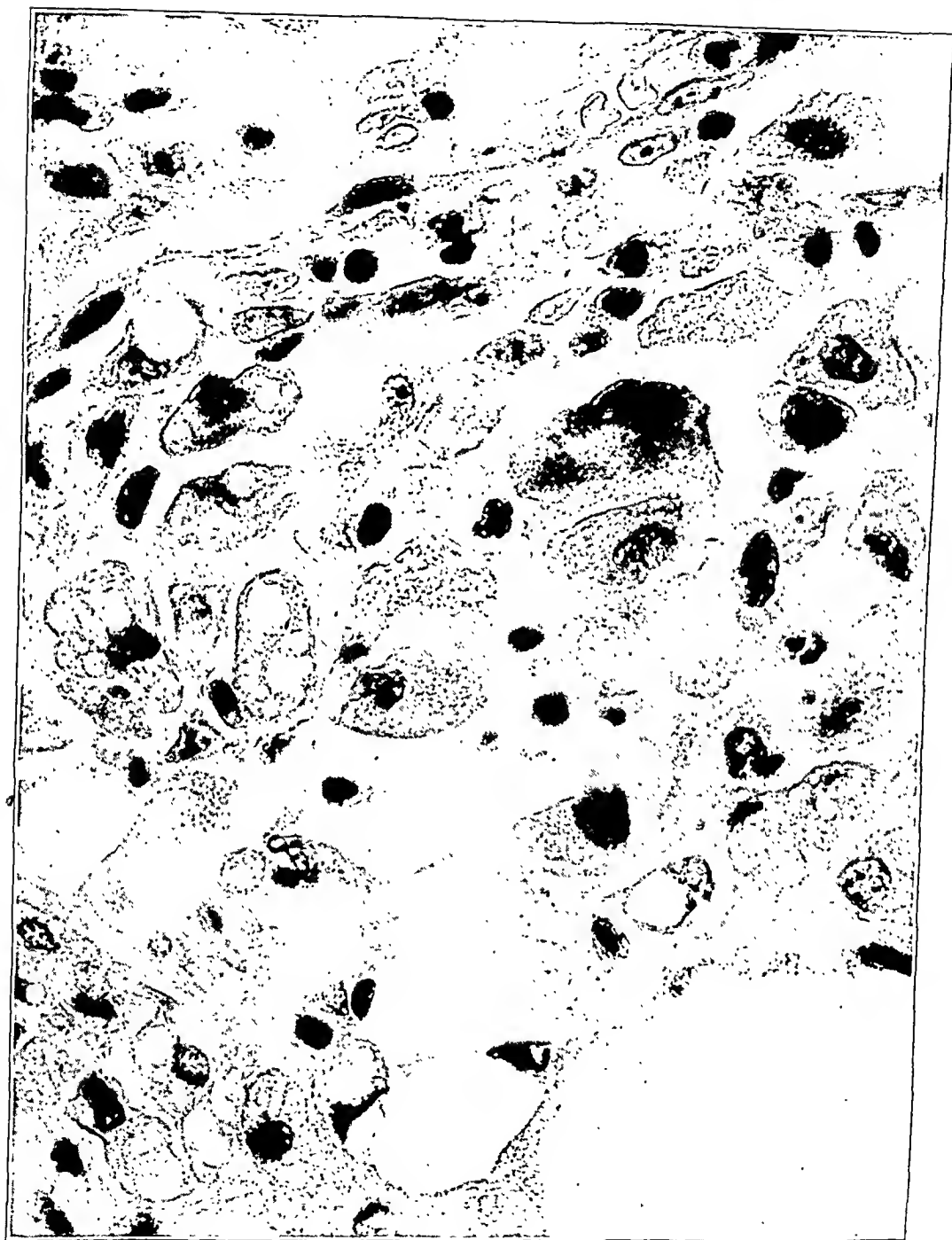
Fig. 6.—Photomicrograph (× 900) showing a marked foreign body reaction with the formation of giant cells in an area of fat necrosis. (Specimen was stained with eosin and methylene blue.)

connective tissue and to some extent of the fat cells (fig. 4). The cellular infiltration may be heavy, and in addition to the mononuclear phagocytes there may be numerous lymphocytes, plasma cells and occasional polymorphonuclear leukocytes (fig. 5). In early fat necrosis, a stage not often seen histologically, polymorphonuclear leukocytes may be numerous. In a later stage, giant cells frequently constitute a prominent feature (figs. 6 and 7), so that in some instances the lesion bears a superficial resemblance to tuberculosis. More commonly, however, as the lesion develops one finds many cystlike areas of necrotic fat, sur-
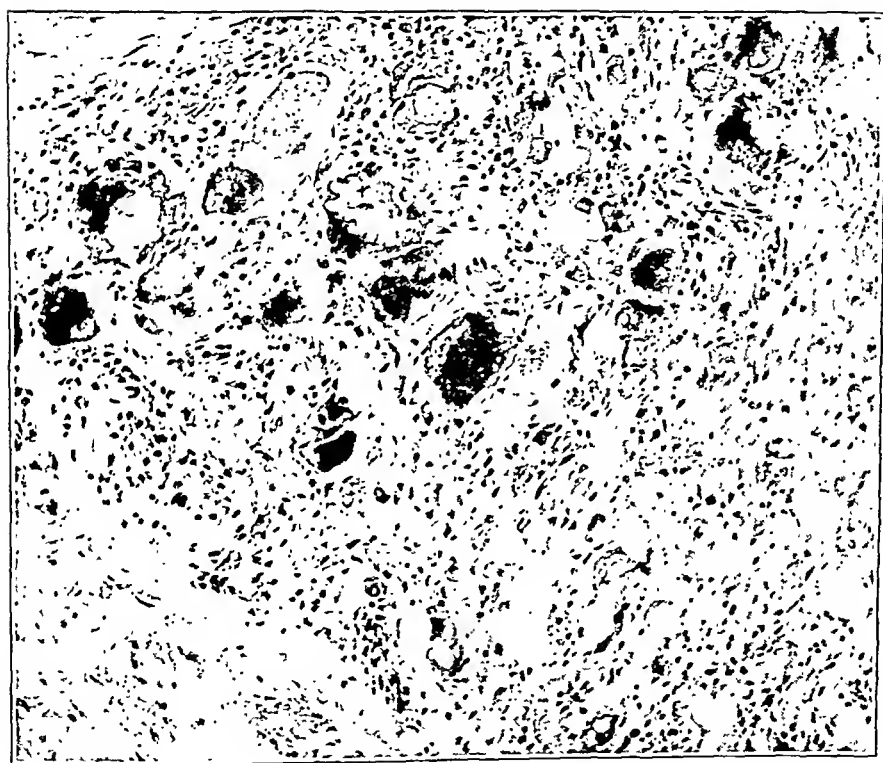
Fig. 7.—Photomicrograph (× 165) showing the formation of numerous giant cells in an area of fat necrosis. Histologically the lesion may bear a resemblance to tuberculosis. Note the fatty acid crystals within the giant cells. (The specimen was stained with eosin and methylene blue.)

rounded by mononuclear phagocytes and giant cells and separated by broad bands of proliferating connective tissue (fig. 8). These cystic areas may become macroscopically visible but rarely exceed 1 cm. in diameter.

Obliterative endarteritis is occasionally associated with fat necrosis, particularly in the late stages. In some cases such vascular changes

may constitute the causative factor. Usually, however, the obliteration
of the vessels is an accompaniment of the contraction and hyalinization of
the connective tissue, which occurs throughout the area of fat necrosis.
In the very late stages the cellular reaction may completely subside,
leaving only the cystlike areas, which are surrounded by dense, hyalin-

Fig. 8.—Photomicrograph (× 165) of advanced fat necrosis. Here one finds
the confluent spaces of necrotic fat surrounded by a wall of phagocytes and giant
cells and separated by broad bands of connective tissue. This is the character-
istic histologic picture of fat necrosis. The pseudocysts become macroscopically
visible but rarely exceed 1 cm. in diameter. (The specimen was stained with
eosin and methylene blue.)

ized acellular scar tissue (fig. 9). In this stage areas of calcification
are not uncommon.

The gross appearance of fat necrosis varies considerably, depending on the stage in which it is observed. Hadfield [7] stated that in the very early stages of fat necrosis the lesion may occupy exactly one or two fat lobules, appearing as a sharply demarcated, opaque area which stands out prominently against the normal fat surrounding it. It is soon followed by central liquefaction of the lesions, and then one finds

Fig. 9.—Photomicrograph of an area of late fat necrosis. The cellular reaction has subsided, and the connective tissue is undergoing hyalinization.

a poorly demarcated, edematous area of fat in which minute cystic spaces are visible and from which yellow, oily material may be expressed.

7. Hadfield, G.: Fat Necrosis of the Breast, Brit. J. Surg. **17**:673-682 (April) 1930.

Later the induration becomes more striking, and the cut surfaces of the lesion contain well defined cavities filled with serous fluid, oily, necrotic fat or a grayish white, chalklike débris. This stage is easily recognized by gross inspection and corresponds to the stage of organization and cyst formation described microscopically (fig. 8). However, as the amount of connective tissue increases a more homogeneous grayish white appearance develops. There is also a gritty consistency, so that the tissue resists the blade of a knife in a manner much like that of scirrhous carcinoma. Even in this stage it is not likely that the experienced observer would mistake fat necrosis for carcinoma, but to one not familiar with it or not suspecting it the condition may prove deceptive. It is possible to interpret areas of necrotic fat as tumor, and in 1 case in the present series the correct diagnosis was in doubt until a histologic examination was made. Consequently, a biopsy with histologic examination of the tissue should be performed for suspected malignant tumor in those areas in which fat necrosis usually is encountered.

CLINICAL MANIFESTSTIONS

The incidence of fat necrosis cannot be accurately estimated because the lesion in many cases is not recognized. A considerable number of such lesions are treated as carcinoma. Thus, Hadfield[7] in a review of 45 collected cases of fat necrosis of the breast found that a radical mastectomy had been performed in 12 per cent. In the files of clinical diagnoses in the Peter Bent Brigham Hospital only 2 cases of extra-abdominal fat necrosis were recorded during the period between 1923 and 1937. In the department of pathology the diagnosis was made 10 times during this period. A study of a number of lesions of fat which had been diagnosed as chronic infection revealed 6 additional cases. An analysis of these 16 cases is outlined in table 1.

Twelve of the patients were females, and 4 were males. The age incidence varied from 16 to 68, the average being 50. One patient was in the second decade of life, none in the third, 5 in the fourth, none in the fifth, 6 in the sixth and 4 in the seventh. There seemed to be no relation between occupation and the development of fat necrosis. All of the patients were white except 1, who was a Negro. Six were described as obese, 9 were well developed and well nourished and 1 was of a thin, asthenic habitus. In this patient (case 10) the lesion was secondary to chronic infection. As one would expect, those patients who have an abundant panniculus are more susceptible to fat necrosis. The duration of the lesion is of no striking diagnostic importance. In the present series the nodule had been known to be present for periods varying from ten days to five years before operation was performed. A history of some form of trauma was mentioned by only 6 of the 16 patients. Only 1 of the patients had syphilis. None had diabetes.

TABLE 1.—Summary of Sixteen Cases of Fat Necrosis

Case	Age Race	Sex	Occupation	Habitus	History	Etiology	Clinical Diagnosis	Pathologic Diagnosis	Treatment	Result
1	52 W	F	Bookkeeper	Well developed	Lump in right breast first noticed 10 days before admission	None discovered	Carcinoma of breast	Fat necrosis	Radical mastectomy	No recurrence
2	61 W	F	Housewife	Obese	Radical mastectomy 9 months before for carcinoma; nodule in operative scar for 1 month	Trauma	Recurrent carcinoma	Fat necrosis	Excision	No recurrence
3	52 W	F	Housewife	Obese	Radical mastectomy for carcinoma 4 months previously; nodule in scar for 2 months	Trauma	Recurrent carcinoma	Fat necrosis	Excision	No recurrence
4	37 W	F	Housewife	Obese	Lump in right buttock first noticed 10 weeks before admission; no pain or tenderness	None discovered	Malignant tumor	Fat necrosis	Biopsy	No further progression of the lesion
5	63 W	F	Housewife	Well developed	Lump in breast of 7 weeks' duration; no pain or tenderness	None discovered	Carcinoma of breast	Fat necrosis	Radical mastectomy	No recurrence
6	16 W	F	Schoolgirl	Well developed	Blow in calf of leg 5 years previously; small nodule near site of trauma ever since	Trauma	Deferred	Fat necrosis	Excision	No recurrence
7	57 W	F	Housewife	Obese	Nodule near site of varicose ulcer for 3 years	Chronic infection and trauma	Varicose ulcer with localized abscess	Chronic inflammation in fat*	Excision	No recurrence
8	63 W	F	Housewife	Well developed	Nodule near site of varicose ulcer for 2 years	Chronic infection and trauma	Abscess in varicose ulcer	Chronic inflammation in fat*	Excision	No recurrence
9	35 W	F	Laundress	Obese	Nodule on palm of hand 3 months after burn	Trauma	Scar tissue	Chronic inflammation in fat*	Excision	No recurrence
10	33 W	F	Manicurist	Thin	Metastatic abscess of thigh, 2 months' duration	Infection	Abscess	Fat necrosis	Incision; drainage; biopsy	No recurrence
11	39 N	M	Laborer	Obese	Lipoma of shoulder, 5 years' duration; frequently traumatized in lifting heavy objects	Trauma	Lipoma	Lipoma with fat necrosis	Excision	No recurrence
12	67 W	M	None	Well developed	Inguinal hernia incarcerated for 4 years	? Ischemia	Hernia	Fat necrosis in preperitoneal fat	Repair of hernia with excision of nodule in preperitoneal fat	No recurrence
13	65 W	F	Housewife	Well developed	Nodule on abdomen for several months	None discovered	"Cyst"	Fat necrosis	Excision	No recurrence
14	32 W	M	Physician	Well developed	Fracture of leg 15 years before; trauma to site of fracture 8 weeks before admission	Trauma	"Nodule" in subcutaneous tissue	Fat necrosis	Excision	No recurrence
15	50 W	F	Housewife	Well developed	Lump beneath the angle of the left jaw	None discovered	Wen	Chronic infection in fat*	Excision	No recurrence
16	50 W	M	Gas fitter	Well developed	Femoral hernia incarcerated	? Ischemia	Hernia	Fat necrosis in omental fat	Excision	No recurrence

* Original histologic diagnosis made in 1923. When the material was reviewed the histologic character of these lesions was found to be that of fat necrosis.

It is remarkable that in none of these cases was the possibility of fat necrosis considered before operation. In 6 a clinical diagnosis of carcinoma was made, and in 2 radical surgical operations without biopsy were done. It would appear that there is need to call attention once again to the varied clinical manifestations of extra-abdominal fat necrosis.

The present series is representative of the various locations in which fat necrosis may arise (table 2). Of these the breast assumes by far the greatest importance. In this location fat necrosis appears as a firm, often painless nodule which gradually or sporadically makes rapid increases in size. It may be situated in any quadrant of the breast. A definite history of trauma has been obtained in only 40 per cent of the reported cases. In more than 50 per cent the lesion has been adherent to the skin, and occasionally the typical "peau d'orange" appearance of cancer has been observed. In 10 per cent there has been retraction of the nipple, and in about the same proportion the lesion

TABLE 2.—*Location of Lesions*

Area Involved	Number of Cases
Breast	2
Postoperative mastectomy scar	2
Lipoma of shoulder	1
Hernial sac (inguinal)	2
Subcutaneous tissue of lower extremity	3
Subcutaneous tissue of lower extremity with varicose ulcer	2
Subcutaneous tissue of upper extremity	1
Subcutaneous tissue of abdominal wall	1
Buttock	1
Subcutaneous tissue of neck	1

has been adherent to the deep tissues of the chest wall. A clinical diagnosis of fat necrosis of the breast is occasionally possible, particularly if after trauma to the breast a mass has developed rapidly and no involvement of the axillary lymph nodes is found. More often, however, the lesion is much like carcinoma in appearance, and only unusual circumspection will prevent an error. This means that for even a "typical carcinoma" of the breast a biopsy must be performed and histologic examination by means of a frozen section must be made before radical surgical treatment is given. Case 1 illustrates the difficulty in diagnosis which fat necrosis may present.

CASE 1.—I. H., a woman aged 52, unmarried, a bookkeeper, was admitted to the hospital because of a lump in the breast, first noticed ten days prior to admission. There was no history of trauma, pain or tenderness in the nodule. There had been no discharge from the nipple. Physical examination disclosed a well preserved woman. In the outer half of the right breast, on a level with the nipple, there was a mass which measured 2 by 1.5 by 1.5 cm. It was firm and slightly irregular but freely movable. There was dimpling of the skin over the nodule. A few small, soft lymph glands were palpated in the axilla. Laboratory studies revealed nothing abnormal. A clinical diagnosis of carcinoma of the breast was made, and operation was advised. At operation an incision was made

into the tumor, and as the gross appearance of the tissue at the depth of the wound seemed characteristic of carcinoma a radical mastectomy was performed. Examination of the specimen after excision disclosed a mass of hard, firm tissue, measuring roughly 4 cm. in diameter, situated in the upper outer quadrant of the breast. Grossly, the lesion was suggestive of carcinoma. Histologic examination, however, revealed a large area of fat necrosis with extensive fibrous tissue reaction at the periphery. There was no evidence of neoplasm.

The development of fat necrosis in a mastectomy scar presents even greater difficulties in diagnosis, particularly if the mastectomy has been performed for carcinoma. There were 2 such cases in the present series, and it is likely that the condition is more common than has been realized. In this situation fat necrosis appears as a hard, irregular nodular growth which is usually fixed to the chest wall. Unless the possibility of fat necrosis is kept constantly in mind a diagnosis of recurrent carcinoma is inevitable. The following cases are examples.

CASE 2.—L. P., a woman aged 64, divorced, was admitted to the hospital because of a nodule in the operative scar of a radical mastectomy which had been performed for adenocarcinoma six months previously at another hospital. The patient was a moderately obese woman in good general health. The physical examination disclosed as the only abnormality a hard, fixed irregular nodule 3 by 1 by 1 cm., in the operative incision. This was fixed to the underlying tissues and was interpreted as a nodule of recurrent carcinoma. At operation this nodule was so widely excised that a plastic procedure was necesary to close the wound.

Gross inspection of a cut surface of the excised tissue revealed numerous small cysts filled with viscid, oily material. A diagnosis of fat necrosis was made, and this was confirmed by histologic examination.

CASE 3.—L. C., a Jewish woman aged 52, a housewife, was admitted to the hospital because of a lump in the left breast, of four weeks' duration. There had been no pain, tenderness or discharge from the nipple. Physical examination showed an obese woman. The breasts were pendulous. There was a hard, slightly irregular nodule in the lower inner quadrant of the left breast. This was freely movable. The axillary nodes were easily palpable and were stony hard. A radical mastectomy was performed for what proved to be adenocarcinoma. Skin grafting was necessary to close the wound. Postoperatively there was much bloody discharge from the wound. There was also considerable sloughing of the skin flaps. The wound healed slowly by secondary intention.

Four months after this operation the patient noticed a small nodule in the upper portion of the scar and came at once to the hospital. At this admission the physical examination showed the patient to be in good general health. There was a bean-sized, irregular, hard but freely movable nodule in the upper portion of the scar. The tissues adjacent to this nodule were firm. A diagnosis of recurrent carcinoma of the breast was made. At operation a rather extensive dissection of the scar tissue was done, and before a histologic diagnosis of fat necrosis was made the surgeon was planning to remove a portion of the chest wall. A frozen section prevented unnecessary surgical intervention, as it showed no evidence of carcinoma.

Such cases as these are an adequate indication for biopsy and histologic examination of the tissue before surgical intervention or irradiation is employed in the treatment of a lesion suspected to be recurrent carcinoma of the breast. It should be noted that fat necrosis may not develop for months or even years after trauma to the normal breast. Hence, in cases in which fat necrosis occurs in mastectomy scars the length of time after operation which elapses before the lesion develops may be variable.

Elsewhere in the body, fat necrosis is less likely to be mistaken for a malignant neoplasm, but it may prove a baffling lesion. The following case is an example.

CASE 4.—L. S., a Canadian-born woman aged 64, a housewife, was admitted to the hospital because of a painful tumor of the right buttock, first noticed ten weeks prior to admission. There was no history of unusual trauma. Since it was first noticed the tumor had not increased in size. The patient sought medical advice because of lancinating pain arising in the region of the growth and radiating down the thigh. Physical examination disclosed an irregular, poorly circumscribed, slightly tender mass just above and lateral to the right ischial tuberosity. The nodule was situated deep in the fatty tissues of the buttock and was firm but not hard. Except for obesity the examination showed no abnormal conditions. The results of laboratory studies were not remarkable. The Wassermann and Hinton tests gave negative results.

At operation a nonencapsulated, hard, gritty tumor was encountered. The cut surface of the lesion was whitish yellow, and the gross appearance suggested malignancy. A frozen section revealed fat necrosis and no evidence of tumor. A radical dissection of the lesion was thus prevented.

Other situations in which fat necrosis may occur are (1) an old incarcerated hernial sac (2) a lipoma and (3) any place where a nodular lesion develops after trauma or long-standing infection. In an old incarcerated hernial sac, either the omentum or the properitoneal fat is involved. This occurs independently of any lesion in the pancreas. Usually the condition manifests itself as a moderate induration of the fat and does not attract the attention of the operator, but in 1 case in the present series there was a solitary whitish gray, firm nodule fixed to the under surface of the hernial sac. It strongly suggested the seeding of an intra-abdominal tumor, and it might easily have led to an unnecessary exploration of the abdomen if its true nature had not been suspected and the diagnosis confirmed histologically. In a lipoma, areas of fat necrosis may impart an irregularly nodular consistency to the tumor, causing it to be mistaken for a sarcoma.

The development of carcinoma in areas of chronic inflammation is a fairly common clinical observation.[8] It is not generally known, however, that occasionally fat necrosis may arise in or adjacent to such areas. In the present series there were 3 instances of such origin, but in each case the small tumor mass which developed was interpreted

as an indurated abscess cavity rather than a neoplasm. However, in view of the similarity which fat necrosis bears to neoplasm elsewhere in the body it is not unlikely that in certain cases it may also simulate malignant disease in this situation.

SUMMARY

Attention is again called to the fact that fat necrosis in the breast or in the subcutaneous tissues may present the clinical aspects of a malignant neoplasm and thus lead to ill advised surgical treatment or irradiation therapy. The etiologic factors and the pathogenesis of this condition are discussed, and its varied clinical manifestations are described. The lesion may be encountered anywhere in the body, but it should be suspected particularly in the presence of pathologic change in the breasts and in mastectomy scars, because in these locations a mistaken diagnosis leads to unnecessarily radical surgical or irradiation therapy. The possibility of fat necrosis must be kept in mind, and biopsy with histologic examination of the tissues must be performed before operation or irradiation therapy is employed for a nonexistent malignant lesion.

8. Harrison, J. H.: Epidermoid Carcinoma in Osteomyelitis: Case Report, Am. J. Cancer **32**:527-533 (April) 1938.

REPAIR OF HERNIA WITH PLANTARIS TENDON GRAFTS

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The plantaris tendon is a suitable structure for grafting and can be used in operations usually performed with grafts of fascia lata, over which it has several advantages. My object in this paper is first to state the relevant facts about the anatomy of the tendon, secondly to describe a method of removing it and thirdly to describe its use as a graft in the repair of hernia.

ANATOMY

The plantaris tendon is absent in 7.5 per cent of subjects, according to Gruber as quoted in Quain's "Anatomy"[1] (1892). In a further proportion of cases it is too slender to be used as a graft in hernia repair, although it may be adequate for other purposes as a suture material. In 100 consecutive postmortem examinations I found the tendon absent or inadequate in 16. This constitutes the sole disadvantage of the proposed use of the tendon. The deficiency, however, is more common in women than in men, and it is for the latter that the graft is mostly required for hernia repair. Moreover, the tendon is often palpable through the skin, and although its absence cannot be inferred when it is impalpable it is often possible to determine that it is present and well developed before an operation is begun.

The plantaris muscle arises from the lateral condyle of the femur, and its long tendon passes obliquely through the calf in the avascular plane between the gastrocnemius and the soleus muscle. This plane is readily opened by blunt dissection. The length of the fleshy part of the gastrocnemius is variable, and when it is short, as much as 6 inches (15 cm.) of the plantaris tendon may be lying subcutaneously on the achilles tendon. Its termination is variable, as also is its relation at the lower end to the achilles tendon. It may have a separate insertion into the calcaneus muscle beside the larger tendon or it may blend with it and share its insertion. In other cases it is inserted into the deep fascia of the leg or into the internal annular ligament. The latter

1. Quain, J.: Elements of Anatomy, ed. 10, edited by A. Schäfer and G. D. Thane, London, Longmans, Green & Co., 1892, vol. 2, pp. 264.

arrangements are usually found with very slender tendons. Quain stated that the plantaris tendon is sometimes enclosed in the lower part of the achilles tendon, but I have not met with this variety either at operation or at postmortem examination. When the two tendons blend to share a common insertion, the plantaris spreads at its lower end into a fan-shaped thin sheet which embraces the achilles tendon (fig. 1). · This is one reason for making the incision to expose the lower end a little above the insertion. Through this incision the tendon will be found in one of three places. Usually it lies closely applied to the medial border of the achilles tendon; if not here it will probably be found in the fat on the medial side, sometimes as much as ½ inch (1.27 cm.) in front of the achilles tendon; rarely it is closely applied to its deep aspect.

The part of the tendon below its emergence from under the gastrocnemius muscle is crossed obliquely by several leashes of blood vessels which might be injured in the proposed method of extraction. There
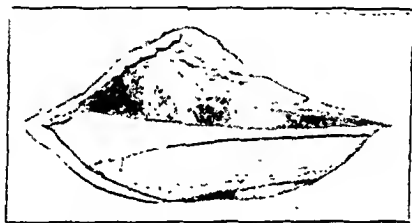
Fig. 1.—Right plantaris tendon exposed at lower end. The tendon lies flat on the achilles tendon, spreading out over its lower end into the shape of a fan.

has been no evidence of this accident in my experience. Sometimes after the extraction of the tendon a few muscle fibers are found adherent about its middle. These come from the soleus, and although easily stripped from the tendon they probably represent a functional attachment, since in such cases the tendon is larger in its lower than in its upper half, whereas the reverse is found when there is no such attachment.

Occasionally the soleus muscle has a small accessory tendon lying medial to and separate from the achilles tendon. This may be mistaken for the plantaris tendon through a small incision, but the mistake may be avoided by noting the greater tension in the short soleus tendon and the presence of muscle fibers entering it (fig. 2).

For the greater part of its course the tendon is lying in loose areolar tissue, allowing easy separation by blunt dissection, but where it passes under the edge of the gastrocnemius it may be held close between that muscle and the soleus tendon, and a little difficulty may be encountered in separating it from them.

The tendon has the curious property of lateral stretching without splitting. Even a slender specimen may be pulled out easily into a sheet 2 inches (5 cm.) wide (fig. 3). A part of this lateral stretching occurs at the expense of length, and if the stretched tendon is pulled in its length it resumes its cordlike form. Use is made of this property in the method of repair of hernia to be described.

METHOD OF EXTRACTING THE TENDON

The leg is held by an assistant, externally rotated so that its medial aspect is exposed. An incision 1 inch (2.5 cm.) long is made over the medial aspect of the achilles tendon a little above its lower end. One reason for thus placing the incision has already been given, i. e.,

Fig. 2.—Accessory soleus tendon found post mortem. *S*, soleus tendon; *P*, plantaris tendon.

that the tendon spreads out into a fan at its insertion and may be difficult to identify. I have also thought it advisable to place the incision so that the scar shall not be subject to pressure from the edge of the shoe. If the tendon is in its most common place it will be exposed by the incision and will be seen lying on the achilles tendon (fig. 1). If not present here it should be sought in the fat antero-medial to the tendon, where it is easily identified if made taut by dorsiflexion of the foot. Finally, it may sometimes be found closely applied to the anterior aspect of the achilles tendon. When found it is cleaned in the length of the wound and divided as low as possible. The cut end is then passed through the eye of the stripper (fig. 4), which is the only special instrument required and is a modification

of Mayo's varicose vein enucleator (fig. 5). The eye of the stripper, threaded over the tendon, is then inserted in the wound and pushed up the leg while tension is maintained on the cut end. Very little resistance is encountered to the passage of the stripper, but it may require a little coaxing about the middle of the tendon, where it lies in the angle at the junction of the gastrocnemius and soleus tendons. The stripper is pushed up until the eye lies just below the popliteal fossa. A second incision, 1 inch (2.5 cm.) long, is now made over the
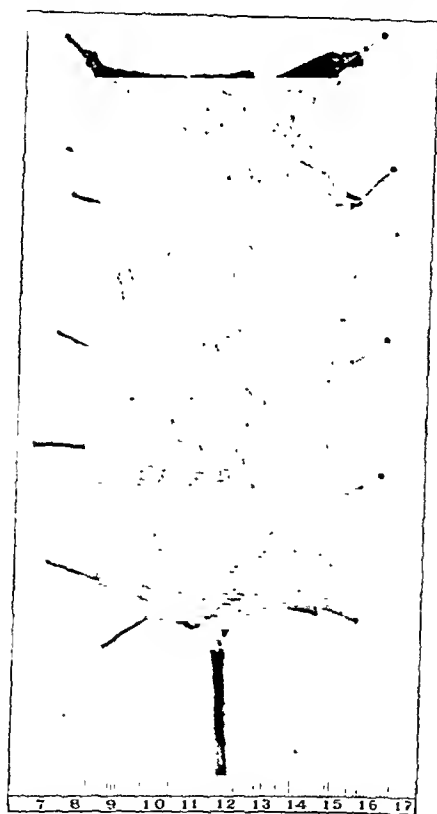
Fig. 3.—Plantaris tendon spread laterally (centimeter scale).

medial edge of the tibia near its upper end where it expands toward its head. This incision is carried through the deep fascia, which is a forward extension of that enclosing the gastrocnemius muscle. The incision in the deep fascia opens the plane between the gastrocnemius and the soleus muscle. The muscles are separated by blunt dissection and held apart with the blades of a large artery forceps (fig. 6A). The assistant by manipulating the handle of the stripper can direct its eye toward the surface of the wound, the tendon at this level being deep because of its oblique course toward the lateral condyle of the .

femur. The tendon is easily identified in the eye of the stripper and is divided as high as possible (fig. 6*B*). Tendon and stripper are then withdrawn through the lower incision, and both incisions are closed. No vessels of any size need be divided by the incisions, the subcutaneous veins in the upper part being usually visible and easy to avoid. At first the upper incision was made on to the eye of the stripper while the assistant directed it to the surface, but this method was abandoned, as it was feared the saphenous nerve might be injured. Because of the possibility of bleeding from the leashes of vessels crossing the lower half of the tendon, a crepe bandage is applied to the leg.
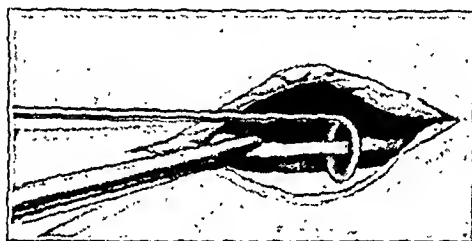
Fig. 4.—*Plantaris tendon exposed at the lower end, divided and threaded through the eye of the stripper.*
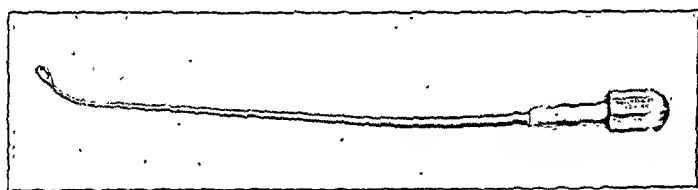
Fig. 5.—Tendon stripper.

METHOD OF HERNIA REPAIR

The tendon is used as a graft and not as a suture. The method of fascial suturing described by Gallie and Le Mesurier[2] in 1924 is open to the objection that the passage of the large needle through aponeurotic structures results in splits which may enlarge and become the openings for recurrent hernia. Recurrent inguinal hernia is usually direct, and tearing of the conjoined tendon after suture to the inguinal ligament probably plays a part in its causation. Apart from the passage of large needles, the risk of tearing also makes it essential to avoid tension, and although Gallie and Le Mesurier deprecated tension in the fascial sutures the approximation of conjoined tendon and inguinal ligament depicted in their paper can rarely be obtained without it. A further objection to their method is that it depends for success on the survival

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2. Gallie, W. E., and LeMesurier, A. B.: Brit. J. Surg. **12**:289, 1924.

of the graft, and although their animal experiments suggested that this might be expected, experience with hernia operations shows that it is by no means certain. The validity of these objections is supported by published results of fascial suture. For example, Burdick and his associates [3] in 1937, reporting 1,485 operations, found a recurrence rate of 29.1 per cent. These authors pointed out that fascial suture was mostly used for difficult cases, but it was for these especially that the method was devised. In many of their cases of recurrence they found no trace of the fascial suture used at the first operation.

The method of repair with plantaris tendon is intended to overcome some of these objections. It is hoped that the tendon will be less readily absorbed than fascia lata, but as yet there is no evidence on
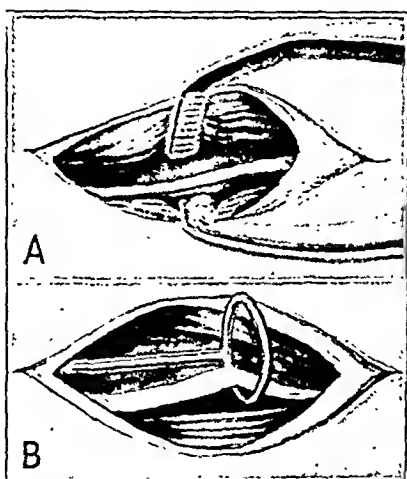
Fig. 6.—*A*, plantaris tendon exposed at the upper end, lying between the soleus and the gastrocnemius muscle. *B*, plantaris tendon directed to the surface of the upper wound with the eye of the stripper.

this point. On the assumption, however, that absorption may occur, the graft is fixed in position with unabsorbable sutures of thread or silk which, acting as foreign bodies, stimulate fibrous tissue which is permanent. Fibrosis stimulated by absorbable agents is not permanent, as can be seen in the treatment of hernia by injection.

After the usual treatment of the sac the inguinal canal is prepared for the graft. In the case of direct hernia the defect in the transversalis fascia is closed with silk or thread. The inguinal ligament and conjoined tendon are cleared of areolar tissue. The proportion of muscle and aponeurosis in the internal oblique and transversalis muscles varies,

3. Burdick, C. G.; Gillespie, D. H. M., and Higinbotham, N. L.: Ann. Surg. **106**:333, 1937.

as has recently been shown by Anson and McVay [4] (1938), and the details of grafting are adapted to suit the conditions found. As far as possible the graft is fixed to aponeurotic rather than muscular structures, and where the internal oblique is muscular it may be better to use the underlying transversalis aponeurosis. Rarely do the muscle
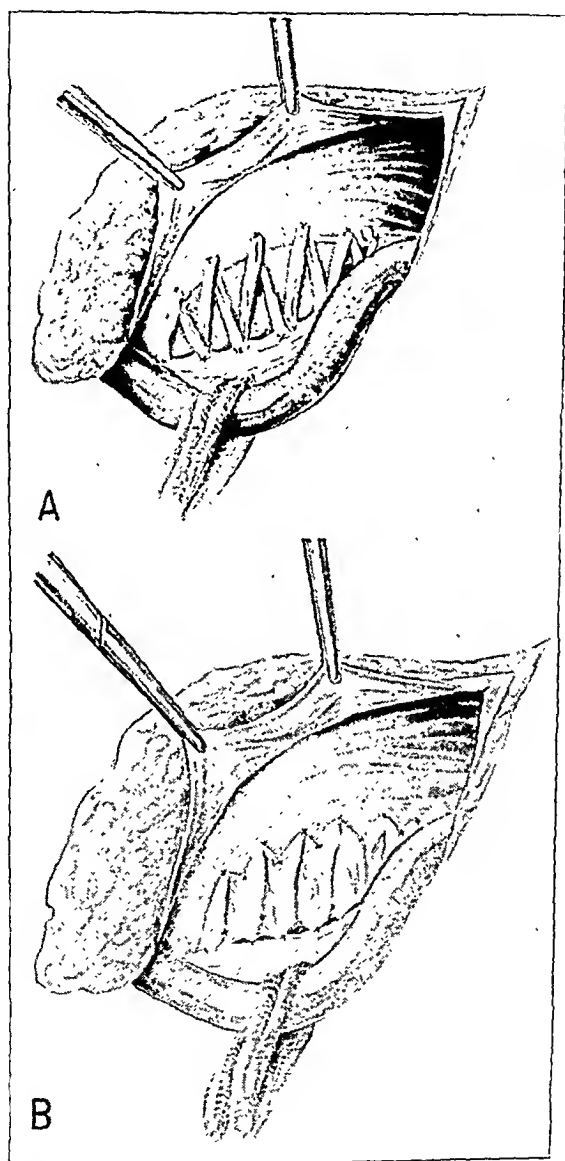
Fig. 7.—*A, graft stitched in position before spreading of the strands. B, adjacent strands of graft spread and sutured to one another.*

fibers of the transversalis extend as low as the spermatic cord. The graft is fixed in a zigzag pattern, being sutured alternately to the inguinal ligament and the conjoined tendon or one of its components with fine silk or thread (fig. 7A). Care must be taken that the

4. Anson, B. J., and McVay, C. B.: Surg., Gynec. & Obst. **66**:186, 1938.

medial angle is adequately covered. There is no tension on the graft, and no attempt is made to approximate the conjoined tendon to the inguinal ligament. The outer end of the graft may be fixed in a loop around the internal ring. After the graft has been fixed in the zigzag fashion, adjacent strands are sutured to one another, the property of lateral stretching allowing this to be done without tension (fig. 7B). In this way the grid of tendon strips is converted into the equivalent of a continuous fascial sheet. The cord is replaced and the wound closed in layers.

The advantages claimed for the method are as follows. The structure used as a graft is removed with very little trauma, and its removal causes no disability. Being tendinous the graft is probably less easily absorbed than fascia. The graft is inserted with minimal trauma to the structures between which it acts as a bridge. It is fixed without tension with unabsorbable sutures; this excites fibrosis which persists even if the graft is absorbed. Lateral stretching of the graft makes approximation of adjacent strands possible without tension.

SUMMARY

The plantaris tendon can be used for operations usually performed with fascia lata.

It lies in a plane that is mainly avascular and can be removed with little trauma through two small incisions over its ends.

It is sometimes absent or inadequate for its proposed use.

In hernia repair it is used as a graft and not as a suture to reenforce the posterior wall of the inguinal canal.

The graft should be fixed with unabsorbable sutures.

Its property of lateral stretching enables the gridlike arrangement of the graft to be converted into a continuous sheet.

SUBDURAL HEMATOMA

DIAGNOSIS AND TREATMENT

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BALTIMORE

In 1925 Cushing and Putnam [1] published reports of 11 cases of subdural hematoma in which the condition apparently arose as the result of trauma to the head. At the same time they summarized the theories regarding the nature of this lesion and discussed its relation to the pachymeningitis haemorrhagica interna described by Virchow.[2] They expressed the opinion that the only pathologic difference between the two is in the microscopic appearance of the membranes of the hematoma, the traumatic form possessing large mesothelial-lined spaces and smaller capillaries. They also concluded that late hemorrhages into the sac are of common occurrence. In 1927 Griswold and Jelsma,[3] in a similar study, concluded that the microscopic appearance of the membranes was the same in both forms. Whatever the relation between the two forms of subdural hematoma, these papers served to emphasize the importance of trauma as a cause, if not the only cause, of the lesion considered in this paper. Such causation is in contradistinction to that of Virchow's pachymeningitis, a condition which occurs in decrepit persons and probably results from systemic causes. Although the microscopic appearance of the membranes is essentially the same with the two types of lesion, the gross lesions are entirely different; with Virchow's pachymeningitis there is solid, thick membrane with little or no blood, and with subdural hematoma these membranes are very thin and the blood is in great volume. As early as 1804, Bell [4] in his "A System of Surgery" wrote of the importance of incising the dura after trephining the skull, for the possible release of subdural blood, in cases of head injuries in which an extradural hemorrhage is not encountered. (There is no record of a case in which the lesion was

1. Putnam, T. J., and Cushing, H.: Chronic Subdural Hematoma, Arch. Surg. **11**:329 (Sept.) 1925.

2. Virchow, R.: Hematoma durae matris, Verhandl. d. phys.-med. Gesellsch. **7**:134, 1857.

3. Griswold, R. A., and Jelsma, F.: Chronic Subdural Hematoma, Arch. Surg. **15**:45 (July) 1927.

4. Bell, B.: A System of Surgery, ed. 3, Philadelphia, T. Dobson, 1806, vol. 2, chap. 10.

cured in this way by Bell.) He further stated that subdural hemorrhages may not give rise to symptoms for several weeks after the injury. The frequency with which cases of traumatic subdural hematoma were reported in surgical papers during the nineteenth century is indicated by the article of Bowen,[5] who in 1905 was able to collect 72 cases (presenting both acute and chronic conditions) from the literature. He divided them into two groups. In the first were those in which the hematomas were unassociated with severe cerebral injury, the hemorrhages apparently having arisen from a tear in a pial vein or a vein running to the longitudinal sinus, and in the second group were those in which the hematomas were associated with severe cerebral lacerations or contusions and produced immediate symptoms. He pointed out that in the first group a period of freedom from symptoms after the injury frequently occurred. Henschen[6] in 1912 also reviewed a series of cases in which the condition was of traumatic origin, and Trotter[7] in 1914 called attention to the fact that the causative injury may be trivial. Subsequently, Rand[8] in 1926 demonstrated that the pial vessels were the source of the hemorrhage in several of his cases. The traumatic origin of this lesion is now widely accepted, as is indicated by the recent papers of Kaplan,[9] Fleming and Jones,[10] McKenzie,[11] Gardner,[12] Fischer and de Morsier,[13] Keegan,[14] Frazier,[15] Coleman,[16] and Furlow.[17] A full discussion of its occurrence in infants is given in a paper of

5. Bowen, W. H.: Traumatic Subdural Hematomas, Guy's Hosp. Rep. 59:21. 1905.

6. Henschen, K.: Diganostik und Operation der traumatischen Subduralblutung, Arch. f. klin. Chir. 99:67, 1912.

7. Trotter, W.: Chronic Subdural Hemorrhage of Traumatic Origin and Its Relation to Pachymeningitis Hemorrhagica Interna, Brit. J. Surg. 2:271, 1914.

8. Rand, C. W.: Chronic Subdural Hematoma, Arch. Surg. 14:1136 (June) 1927.

9. Kaplan, A.: Chronic Subdural Hematoma, Brain 54:430, 1931.

10. Fleming, H. W., and Jones, O. W., Jr.: Chronic Subdural Hematoma. Surg., Gynec. & Obst. 54:81, 1932.

11. McKenzie, K. G.: Surgical and Clinical Study of Nine Cases of Chronic Subdural Hematoma, Canad. M. A. J. 26:534, 1932.

12. Gardner, W. J.: Traumatic Subdural Hematoma with Particular Reference to the Latent Interval, Arch. Neurol. & Psychiat. 27:847 (April) 1932.

13. Fischer, R., and de Morsier, G.: Chronic Subdural Hematoma Following Cranial Trauma, Presse méd. 41:1517, 1933.

14. Keegan, J. J.: Chronic Subdural Hematoma, Arch. Surg. 27:629 (Oct.) 1933.

15. Frazier, C. H.: Surgical Management of Chronic Subdural Hematoma. Ann. Surg. 101:671, 1935.

16. Coleman, C. C.: Chronic Subdural Hematoma, Am. J. Surg. 28:341, 1935.

17. Furlow, L. T.: Chronic Subdural Hematoma, Arch. Surg. 32:688 (April) 1936.

TABLE 1.—*Summary Report of Forty-Eight*

	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes
	26 M W	Headache; vertigo; failing vision; failing hearing; tinnitus	No history of trauma	14 mo.	0	+	+	0	0	+	0	0	0	Bilateral 5 to 6 D; nearly blind	Hearing impaired both ears	0
6	3S M W	Headache	Fall; unconscious; 8 weeks	8 wk.	0	+	+	+	0	0	0	0	0	Bilateral 6 D with hemorrhages	0	0
6	55 M W	Headache; drowsiness	Auto accident; not unconscious; 7 weeks	6 wk.	1 wk.	+	+	÷	0	+	0	0	0	Bilateral 3 D	0	0
	24 M W	Headache; drowsiness; earache	Fall with unconsciousness; 4 weeks	4 wk.	0	+	0	0	0	0	0	0	0	Bilateral 2 D	0	0
16	47 M W	Headache; vomiting	Kicked on head by horse; unconsciousness; 3 years ?	2 yr.?	1 yr.?	+	+	0	0	0	0	0	0	Bilateral	0	0
20	18 M W	Headache; vomiting	No history of trauma	10 wk.	0	+	+	0	0	+	0	0	0	Bilateral	0	Slight weakness of right side
/22	26 M W	Headaches; drowsiness	Struck on left side of head boxing; 6 months	6 mo.	0	+	0	+	0	0	0	0	0		0	0
/23	44 M W	Headache; drowsiness; paralysis right side	Struck head on auto fender; 3 weeks	2 wk.	1 wk.	+	0	+	0	+	0	+ 24 hr.	0	Bilateral papilledema	0	Flaccid paralysis right arm and leg
/34	9 mo. F W	Enlargement of head; convulsions	Birth injury ?	5 mo.	0	0	0	0	0	0	+	0	0	0 .	0	Slight weakness left arm and leg
S. 5/25	64 M W	Headache; mental confusion; drowsiness	Struck by auto; dazed; 8 weeks	8 wk.	0	+	+	+	+	+	0	+	+	0	0	0
1 C. /25	30 M W	Headache; drowsiness	Struck by "knucks"; unconscious; 5 weeks	5 wk.	0	+	+	+	0	0	0	+	0	Bilateral	0	0
2 G. /25	40 M N	Headache; weakness of legs	Struck by auto; unconscious; 9 weeks	3 wk.	6 wk.	÷	0	0	0	0	0	0	0	0	0	Marked muscular weakness, unable to walk
12 B. 13/25	37 M W	Headache; drowsiness	Struck head in fall; 6 months	6 mo.	0	+	+	+	0	+	0	+	+	Bilateral 1 D	0	0
14 S. 21/25	47 M W	Headache; weakness right side; unable to talk	Struck head in fall; unconscious; 5 weeks	4 wk.	1 wk.	+	0	+	0	0	0	0	0	0	0	Spastic paralysis right arm and leg; unable to talk
15 A. /30/26	53 M W	Headache; drowsiness	0	8 wk.	0	+	+	+	+	+	0	0	+	Bilateral papilledema	0	Marked muscular weakness, unable to stand or walk
16 S. /10/26	43 M W	Headache	0	6 mo.	0	+	+	+	+	0	0	0	0	0	0	0
17 J. H. /31/26	32 M W	Drowsiness	Auto accident; unconscious 10 hours; 9 weeks	4 wk.	5 wk.	÷	+	+	0	0	0	0	0	Bilateral papilledema	0	Left facial weakness (central)

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
Deep reflexes hyperactive on both sides	T 98.6 F. P 60 WBC 6,400	Bulging right subtemporal decompression; operated on elsewhere 4 months previously	Erosion posterior clinoids	Tumor of the brain	0	Right craniotomy Mar. 14, 1914; drains used	0	Discharged well Apr. 9, 1914	Died one year later; cause unknown
Deep reflexes more active on left	T 98 F. P 60	0	Normal	Tumor of the brain	0	Right subtemporal decompression; drains used; Apr. 23, 1916	0	Discharged well May 16, 1916	Well in 1937
Deep reflexes more active on left; Babinski sign on left	T 101.8 F. P 60 BP 130/80 WBC 15,000	0	0	Tumor of the brain	0	Right subtemporal decompression; drains used; Oct. 22, 1916	0	Discharged well Nov. 23, 1916	Died in 1932 of cardiac disease
Deep reflexes hyperactive	T 98.6 F. P 66 BP 100/70	0	Fracture at base	None given	0	Right subtemporal decompression; drains used; Dec. 16, 1916	0	Discharged well Dec. 30, 1916	0
Deep reflexes more active on left	BP 145/105 WBC 8,400	0	Normal	Tumor of the brain	0	Right craniotomy; drains; Dec. 27, 1916	0	Discharged well Jan. 11, 1917	History confusing as to when present illness began; well in 1937
Deep reflexes more active on left; Babinski sign on right	T 98.6 F. P 90	0	0	Tumor of the brain	÷	Right craniotomy; drains; Sept. 20, 1920	0	Discharged well Oct. 8, 1920	Homolateral signs; well in 1937
Babinski sign on left	T 98.6 F. P 60 BP 95/50 WBC 11,200	Head is described as being very large	0	Tumor of the brain	÷ Dec. 22, 1922	Left craniotomy; drains; Dec. 26, 1922	÷ Subdural clot evacuated Dec. 28, 1922	Discharged well Jan. 13, 1923	Homolateral signs
Deep reflexes more active on right; Babinski sign on right	T 103.6 F. P 70 WBC 15,000	0	0	Cerebral tumor	0	Left craniotomy; drains; June 20, 1923	0	Died June 21, 1923	Autopsy showed no recurrence of hematoma; brain edematous
0	T 98.6 F.	Enlargement of head; right side larger than left; separation sutures	Hydrocephalus	Hydrocephalus	÷	Right tap subdural space; 80 cc. obtained; May 6, 1924	0	Discharged well June 4, 1924	Well in 1933
Romberg sign	T 98.6 F. P 58	0	0	Brain abscess or cerebral tumor	Trephine revealed hematoma, frontal	Right subtemporal decompression; drains; Feb. 15, 1925	Right craniotomy Feb. 25, 1925; removal bone flap Feb. 27, 1925	Discharged well Apr. 4, 1925	Subtemporal decompression insufficient for complete evacuation
0	T 99.2 F. P 60	0	0	Subdural hematoma	Trephine revealed hematoma	Left craniotomy May 27, 1925	÷ Evacuation extradural hematoma May 29, 1925	Discharged well June 22, 1925	Well in 1937 save for focal epilepsy
Bilateral Babinski sign	T 98.6 F. P 60 BP 170/100	0	Normal	Tumor of the brain	÷	Left craniotomy July 30, 1925	0	Discharged well Aug. 7, 1925	
0	T 98.6 F. P 46	0	Normal	Subdural hematoma	÷	Left craniotomy, Nov. 13, 1925 120 cc. old blood	0	Discharged well Nov. 26, 1925	Well in 1937
Deep reflexes more active on right; Babinski positive on right side; stiff neck	T 98.6 F. P 80 WBC 20,000	0	Normal	Brain abscess	Trephine revealed hematoma frontal	Left craniotomy Nov. 25, 1925	Explored Dec. 1, 1925; extra- and subdural clots	Discharged well Feb. 2 1926	Well in 1937
Bilateral Babinski sign	T 99 F. P 46 BP 105/50 WBC 15,000	0	Normal	Tumor of the brain	÷	Left craniotomy Mar. 21, 1926	0	Discharged well Apr. 15, 1926	Patient epileptic before hematoma; no convulsions during present illness; well in 1937
Bilateral Babinski sign	T 98.6 F. P 56 BP 117/70	0	Normal	Tumor of the brain	Trephine disclosed hematoma frontal	Left craniotomy July 12, 1926	Evacuation extra- and subdural hemorrhage July 13, 1926	Discharged well July 26, 1926	Well in 1937
Deep reflexes more active on left	T 98.6 F. P 60 BP 106/70	0	0	Subdural hematoma	Trephine disclosed hematoma	Bilateral craniotomy Sept. 15, 1926	0	Discharged well Oct. 29, 1926	Bilateral hematoma

TABLE 1.—*Summary Report of Forty-Eight*

Patient and Date of Admission	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes
18 W. W. 11/15/26	57 M W	Headache; drowsiness	0	4 mo.	0	+	+	+	+	0	0	+ 12 hr.	0	0	0	0
19 F. W. 12/27/26	20 M W	Headache	Struck on head in football game; 3 months	3 mo.	0	+	+	0	+	0	0	0	0	Bilateral 2 D	0	0
20 J. E. 11/24/27	59 M W	Headache; vomiting	0	4 mo.	0	+	+	0	0	+	0	0	+	0	0	0
21 F. F. 5/18/28	43 M W	Headache; drowsiness	0	6 wk.	0	+	0	+	0	0	0	Periods of coma	0	Bilateral less than 1 D	Left ptosis (iii)	Left facial weakness (central)
22 C. A. 11/28/28	26 M W	Headache; vomiting	Struck on head with bare fists; 8 weeks	5 wk.	3 wk.	+	+	0	0	+	0	0	0	Bilateral 1 D	0	0
23 C. B. 3/15/29	52 M N	Headache; vertigo	0	5 wk.	0	+	0	0	0	+	0	0	0	Bilateral with hemorrhages	0	0
24 J. O. 3/16/29	29 M W	Headache; loss of vision	Auto accident; unconscious; 1 year	1 yr.	0	+	0	+	+	+	0	0	0	Optic atrophy; blind	Anisocoria; right pupil larger than left	0
25 W. W. 4/16/29	24 M N	Headache; vomiting	Punched about head in boxing; 6 weeks	6 wk.	0	+	+	0	0	0	0	0	0	Bilateral 1 D	0	0
26 R. G. 9/24/29	18 M W	Headache; diplopia	0	3 wk.	0	+	+	0	+	+	0	0	0	Bilateral 1 D	Right facial (vii); absent corneal, left; motor V left; nystagmus	0
27 F. P. 12/20/29	61 M W	Headache; vomiting	0	4 wk.	0	+	+	+	0	0	0	0	0	0	Nystagmus	0
28 W. M. 6/11/30	70 M W	Weakness and numbness of left extremity	0	6 mo.	0	0	0	+	0	0	0	0	0	0	0	Motor weakness of entire left side
29 L. F. 6/11/30	38 F W	Headache; vomiting; tinnitus	0	6 mo.	0	+	+	0	+	0	+ Right focal	0	0	Bilateral 1 D; hemorrhages	0	Slight weakness of right arm
30 M. R. 5/15/31	53 F W	Headache; vomiting; drowsiness	Struck head during paroxysm of sneezing; 3 weeks	2 wk.	1 wk.	+	+	+	+	0	0	0	0	0	Bilateral ptosis; inability to look up; sluggish pupils (iii)	0
31 H. P. 6/15/31	53 M W	Headache	Struck by auto; unconscious; 4 months	4 mo.	0	+	0	+	0	0	0	0	0	0	0	Hypesthesia left extremities; paresis entire left side
32 S. H. 7/18/31	19 M W	Headache; staggering	0	8 mo.	0	+	+	0	0	+	0	0	+	Bilateral 2 D	0	General muscular weakness
33 J. W. 1/23/32	67 M N	Headache; drowsiness	Struck head in fall; unconscious; 5 weeks	5 wk.	0	+	0	+	0	0	0	0	0	0	0	General muscular weakness
34 E. H. 6/28/32	51 M W	Headache; fainting spells	Struck head in fall; unconscious; 3 months	3 mo.	0	+	0	0	+	+ Focal right extremity	0	0	0	Bilateral 3 D; hemorrhages	Nystagmus; right pupil larger than left	0

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
Deep reflexes more active on left; bilateral Babinski sign	T 99.8 F. P 52 BP 120/75 WBC 9,000	Arteriosclerosis of peripheral vessels	Normal	Tumor of the brain	+	Right craniotomy Nov. 16, 1926	Nov. 18 evacuation extradural hemorrhage; Nov. 19 decompression	Discharged well Jan. 11, 1927	Small; removed intact with membrane
0	T 99 F. P 60 BP 110/60 WBC 5,400	0	0	Tumor of the brain	÷	Left craniotomy Dec. 28, 1926	0	Discharged well Jan. 11, 1927	Well in 1937
0	T 98.6 F. P 58 BP 105/70 WBC 16,000	Arteriosclerosis of peripheral vessels	0	Tumor of the brain	÷	Right craniotomy Nov. 26, 1927	Evacuation extra- and subdural hemorrhage Nov. 29, 1927; same Dec. 2 1927	Discharged well Dec. 14, 1927	Well in 1937
Deep reflexes more active on left	T 98.6 F. P 60 BP 150/120	Arteriosclerosis of peripheral vessels	Normal	Tumor of the brain	Trephine disclosed hematoma	Left craniotomy May 21, 1928	0	Discharged well June 14, 1928	
0	T 98.6 F. P 62 BP 100/60 WBC 8,400	0	Normal	Tumor of the brain	÷	Right craniotomy Nov. 30, 1928	Evacuation extra- and subdural hemorrhage Dec. 2, 1928	Discharged well Dec. 22, 1928	
0	T 98.6 F. P 60 BP 115/70 WBC 5,800	0	Normal	Tumor of the brain	÷	Left craniotomy Mar. 19, 1928	Evacuation extra- and subdural hemorrhage Mar. 21, 1929	Discharged well Apr. 1, 1929	Well in 1937
0	T 98.6 F. P 74 BP 90/60	0	0	Pituitary tumor	÷ Cisternal air injection	Left craniotomy Mar. 24, 1929 (hematoma about sella)	0	Discharged improved Apr. 10, 1929	
0	T 98.2 F. P 58 BP 115/70 WBC 7,800	0	0	Subdural hematoma	Trephine disclosed hemorrhage, occipital	Left subtemporal decompression Apr. 19, 1929	0	Discharged well May 15, 1929	
0	T 99 F. P 100 BP 120/80 WBC 6,800	0	Normal	Tumor of the brain	÷	Left craniotomy Sept. 25, 1929	0	Discharged well Oct. 7, 1929	5,000,000 R.B.C. bloody cerebrospinal fluid; hydroma associated with hematoma; well in 1937
0	T 97 F. P 66 BP 190/100	0	Normal	Tumor of the brain	+	Left craniotomy Dec. 20, 1929	Evacuation extra- and subdural hemorrhage Dec. 21, 1929; also twice more with removal bone flap	Discharged well Jan. 21, 1930	Died in 1935 angina pectoris
Deep reflexes more active on left; Babinski positive on left	T 98.6 F. P 60 BP 140/100 WBC 7,300	Arteriosclerosis of peripheral vessels	0	Cerebral hemorrhage	+	Right craniotomy June 14, 1930	Exploration: evacuation bloody fluid June 17	Died June 23, 1930; staphylococcus wound infection; meningitis	Autopsy; no abnormality noted save meningitis and membrane of hematoma; no recurrence
Deep reflexes more active on right	T 98.6 F. P 90 BP 100/65 WBC 7,400	0	Normal	Tumor of the brain	±	Left craniotomy June 1930	0	Discharged well June 23, 1930	
Deep reflexes hyperactive; bilateral Babinski	T 99 F. P 60 BP 140/90	0	Normal	Tumor of the brain	±	Left craniotomy May 16, 1931	Evacuation extra- and subdural hemorrhage May 17; same and removal bone flap May 19	Discharged well June 4, 1930	Bleeding and clotting time normal; well in 1937
Deep reflexes more active on left side; bilateral Babinski	T 99 F. P 60 BP 98/62 WBC 7,900	Tenderness right frontal region	0	Subdural hematoma	0	Right craniotomy June 15, 1931	0	Discharged well June 30, 1931	Well in 1937
0	T 99.6 F. P 62 BP 90/50 WBC 8,000	0	Normal	Tumor of the brain	±	Right craniotomy July 21, 1931	0	Discharged well Aug. 4, 1931	Well in 1937
Deep reflexes hyperactive; bilateral Babinski	T 100 F. P 60 WBC 10,400	Arteriosclerosis of peripheral vessels	Normal	Cerebral hemorrhage	÷	Left craniotomy Jan. 26, 26, 1932	0	Discharged well Feb. 2, 1932	Died 3½ years later of intestinal obstruction; no autopsy on head
0	T 99.6 F. P 80 WBC 6,000	0	0	Subdural hematoma	0	Left craniotomy June 23, 29, 1932	0	Discharged well July 6, 1932	Well in 1937

TABLE 1.—*Summary Report of Forty-Eight*

Patient and date of admission	Age, Sex, Race	Chief Symptoms	Type of Trauma Time Before Admission	Duration of Symptoms	Latent Interval	Headache	Nausea or Vomiting	Drowsiness	Diplopia	Vertigo	Convulsions	Coma	Mental Confusion	Papilledema Retinal Hemorrhages	Involvement of Other Cranial Nerves	Motor and Sensory Changes
35 J. D. /25/32	65 M W	Headache; unconscious spells	Fall from a horse; unconscious; 3 months	3 mo.	0	+	+	+	0	+	+	0	+	0	0	0
36 J. H. ·/13/32	59 M W	Unconsciousness	Struck head in fall; unconscious; 1 week	1 wk.	0	+	0	+	0	0	0	+ 12 hr.	0	0	0	Deep reflexes bilaterally hyperactive
37 P. F. 5/1/33	36 M W	Headache; drowsiness; tinnitus	In auto accident; unconscious; 6 weeks	6 wk.	0	+	+	+	0	0	0	0	0	Bilateral 2 D; hemorrhages	Absent corneal reflex left (v)	Hpyesthesia all extremities; loss of sense of position of toes bilateral
38 J. P. 5/2/34	67 M W	Headache; drowsiness; mental confusion	0	5 mo.	0	+	0	+	0	0	0	0	+	0	0	Slight weakness of left side
39 E. B. 5/12/34	53 F W	Headache	Struck head on bureau; 2 months	5 wk.	3 wk.	+	0	0	0	0	0	0	0	0	0	General muscular weakness; unable to stand
40 R. B. 6/23/34	62 M W	Headache; drowsiness; mental confusion	0	2 mo.	0	+	0	+	0	0	0	0	+	0	0	General muscular weakness; unable to stand
41 E. A. 9/15/34	64 F W	Headache; drowsiness	Struck head on wall; 3 weeks	2 wk.	1 wk.	+	+	+	0	0	0	+ 24 hr.	0	0	0	0
42 C. W. 10/31/34	47 M W	Headache; vomiting	In auto accident; unconscious; 3 months	5 mo.	0	+	+	+	+	0	0	0	0	0	Right vi nerve palsy	General weakness; unable to stand
43 R. C. 11/20/34	8 M W	Headache; vomiting; photophobia	In auto accident; left eye discolored; 3 months	11 days	7 wk.	+	+	+	0	0	0	0	0	Bilateral loss 1 D; hemorrhages	0	0
44 A. H. 11/28/34	9 mo. M N	Drowsiness; convulsions	Fall from bed; 1 week	3 days	4 days	0	0	+	0	0	+	+ 24 hr.	0	Bilateral with hemorrhages	0	Right facial weakness (central type)
45 H. K. 2/9/36	17 M W	Headache; drowsiness	0	1 wk.	0	+	+	+	+	0	0	0	0	Bilateral 4 D with hemorrhages	0	General muscular weakness; unable to stand
46 W. R. 3/3/36	55 M W	Headache; drowsiness	Fall on sidewalk; 6 weeks	6 wk.	2 days	+	+	+	+	0	0	0	+	0	Pupils sluggish	0
47 R. W. 9/5/36	38 M W	Headache, left and general; blurred vision; vertigo	Struck on head with brick; unconscious; 4 weeks	4 wk.		0	+	+	+	0	+	+	0	0	Bilateral 7-8 D	0	0
48 H. R. 7/9/37	59 M W	Headache; convulsion	Fall 8 weeks before admission; not unconscious	3½ wk.	2½ wk.	0	0	0	0	0	0	0	0	0	0	0

Reflex Changes	Temperature, Pulse, Blood Pressure, W.B.C.	Other Positive Findings	Roentgen Findings	Clinical Impression	Trephine Ventriculography	Side of Lesion Type of Operation and Date	Recurrence After Operation	Result	Comment
Babinski sign on right	T 99.2 F. P 50 BP 90/50	Arteriosclerosis of peripheral and retinal vessels	Normal	Cerebral arteriosclerosis	÷	Left craniotomy Aug. 2, 1932	0	Discharged well Aug. 14, 1932	Well in 1937
Babinski sign on right; ankle clonus on right	T 100.6 F. P 80 BP 150/80	Arteriosclerosis of peripheral vessels	0	Subdural hematoma	Trephine disclosed hematoma	Left craniotomy Aug. 13, 1932 (membranes very thin)	0	Discharged well Aug. 23, 1932	Alcoholic; died in 1933 of stricture of esophagus
Deep reflexes hyperactive bilaterally; cervical rigidity	T 99 F. P 54 BP 130/90 WBC 8,000	0	Normal	Subdural hematoma	Puncture	Left craniotomy; right subtemporal decompression; May 6, 1933	0	Discharged well May 23, 1933	Bilateral hematoma; well in 1937 save for slight degree of optic atrophy
Deep reflexes hyperactive; bilateral Babinski sign	T 99 F. P 54 BP 130/90 WBC 7,900	Arteriosclerosis of peripheral and retinal vessels	Normal	Tumor of the brain	Trephine disclosed hematoma, occipital	Left craniotomy May 3, 1934	Evacuation extra- and subdural hemorrhage; decompression May 4, 1934	Discharged well May 21, 1934	Well in 1937
Deep reflexes hyperactive bilaterally; bilateral Babinski sign	T 99 F. P 58 BP 130/80 WBC 6,600	0	Normal	Tumor of the brain	÷	Left craniotomy May 15, 1934	Evacuation extra- and subdural hemorrhage; decompression May 16, 1934	Discharged well June 3, 1934	Well in 1937
Deep reflexes hyperactive	T 98.6 F. P 56 BP 140/90 WBC 6,600	Arteriosclerosis of peripheral vessels	Normal	Tumor of the brain	÷	Left craniotomy June 25, 1934	Evacuation extra- and subdural hemorrhage; decompression July 3, 1934	Discharged well July 9, 1934	Well in 1937
Babinski sign on right	Not recorded	Arteriosclerosis of peripheral vessels	0	Tumor of the brain	÷	Left craniotomy Sept. 15, 1934	Evacuation extra- and subdural hemorrhage; decompression; Sept. 16, 1934	Discharged well Sept. 28, 1934	
Deep reflexes more active on left	T 99 F. P 66 BP 140/90 WBC 10,400	0	Normal	Tumor of the brain	÷	Right craniotomy Nov. 2, 1934	0	Discharged well Nov. 12, 1934	History of some headache preceding auto accident by 2 months; well in 1937
0	T 99 F. P 72 BP 90/60 WBC 8,800	Tenderness to pressure left side of skull; cervical rigidity	0	Tumor of the brain	÷	Left craniotomy Nov. 21, 1934	0	Discharged well Nov. 28, 1934	175 cc. fluid blood; few clots; hgb. 103%; RBC 4,100,000; WBC 6,100; NPN 28 mg.; NaCl 552 mg.; sugar 40 mg.; total protein 5.6; albumin-globulin ratio 65/35; well in 1937
Bilateral Babinski sign	T 101 F. WBC 12,000	0	0	Subdural hematoma	Puncture of subdural space	Left craniotomy; decompression; Nov. 30, 1934	0	Discharged well Jan. 3, 1935	Died in fire 2 months later
0	T 100 F. P 48 BP 120/80 WBC 14,500	0	Normal	Tumor of the brain	÷	Left craniotomy Feb. 11, 1935	0	Discharged well Feb. 20, 1935	Well in 1937
Deep reflexes more active on right; bilateral Babinski sign	T 98.6 F. P 60 BP 170/100	Arteriosclerosis	Normal	Subdural hematoma	÷	Left craniotomy Mar. 4, 1936; 12 hours later decompression	0	Discharged well Mar. 13, 1936	Small hematoma, 40 cc. blood laked; sugar 25 mg.; NPN 28 mg.
0	T 98.6 F. P 70-90 BP 120/80	0	0	Subdural hematoma	÷	Left craniotomy Sept. 8, 1936	0	Discharged well Sept. 16, 1936	Small hematoma, 40 cc. blood laked; NPN 28 mg. per 100 cc.
0	T 98.6 F. P 90 BP 150/100 WBC 8,000	0	Normal	Subdural hematoma	÷	Left craniotomy July 9, 1937	0	Discharged well July 21, 1937	Small hematoma, 40 cc. or less; no RBC in fluid

Sherwood's [18] in 1930, although in none of his cases was there a history of trauma. Peet and Kahn [19] in 1932 pointed out the importance of operative intervention in cases in which the patients are infants and children. Jelsma [20] in 1930 summarized the symptoms and clinical findings in 42 surgical cases previously reported in the literature and added 2 cases of his own. It is apparent that subdural hematoma is recognized more frequently than formerly, although the number of surgical cases reported is still rather small.

In the neurosurgical service of the Johns Hopkins Hospital between 1914 and 1935 there have been 48 cases of subdural hematoma in which the lesions at operation were found to have the characteristics of the traumatic hematomas described by others.[21] The first case was described by Heuer and Dandy [22] in 1916. That there may have been others in which the condition was unrecognized is likely only before the introduction of ventriculography by one of us· (W. E. D.) in 1918. Prior to that time a right subtemporal decompression was frequently performed on patients suspected of having a tumor of the brain but not having localizing signs. The lesions in cases 2, 3 and 4 were apparently discovered during such an operation, and had the hematomas occurred on the left side it is readily seen that they would have escaped recognition. With the aid of ventriculography the diagnosis and localization of such a lesion has been greatly simplified.

Age.—Of the 48 patients 40 were adults, 6 were minors and 2 were infants each 9 months of age. The largest number of hematomas (11) occurred in the sixth decade of life, and the smallest number (3) occurred in the first decade. Five occurred in the second decade. That the lesion occurs occasionally in young persons has been recognized before. The average age for the entire group was 41.2 years. Jelsma in his analysis of 42 cases found an average age of 39.2 years and a fairly similar age distribution.

Sex.—There were 43 male and 5 female patients, a disproportion encountered in all other case reports and doubtless correctly attributed to the accepted cause, that is, trauma.

Color.—Forty-four patients were white, and 4 were Negroes.

18. Sherwood, D.: Chronic Subdural Hematoma in Infants, Am. J. Dis. Child. **39**:980 (May) 1930.

19. Peet, M. M., and Kahn, E. A.: Subdural Hematoma in Infants, J. A. M. A. **98**:1851 (May 28) 1932.

20. Jelsma, F.: Chronic Subdural Hematoma: Summary and Analysis of Forty-Two Cases, Arch. Surg. **21**:128 (July) 1930.

21. Putnam, T. J., and Putnam, I. K.: The Experimental Study of Pachymeningitis Hemorrhagica, J. Nerv. & Ment. Dis. **65**:260, 1927.

22. Heuer, G., and Dandy, W. E.: A Report of Seventy Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224, 1916.

Side of Occurrence of the Hematoma.—In 30 cases, or 61.7 per cent, the hematoma was on the left side, and in 15, or 32.1 per cent, it was on the right. In 2 cases, or 4.2 per cent, the lesion was bilateral. We can think of no reason for assuming that the much greater incidence of this lesion on the left side has any anatomic significance. In 1 case it lay about the sella turcica.

Cause.—That an injury to the head is generally regarded as the cause of this lesion has already been mentioned. Furthermore, the frequency with which subdural hemorrhages accompany severe injuries to the head has recently been emphasized by Leary [23] and Munro.[24] These authors and Coleman [16] included the "acute" lesions in their analysis of the subject. In this series, however, patients with fresh subdural clots, showing immediate symptoms of severe injury requiring prompt operative intervention, have been excluded because from a clinical standpoint they fall under the classification of patients suffering from the immediate effects of acute injury to the head.

TABLE 2.—*Age Incidence in Decades*

Age, Years	Number of Cases	Percentage
0-10	3	6.3
10-20	5	10.6
20-30	6	12.7
30-40	7	15
40-50	7	15
50-60	12	23.4
60-70	8	17
Average age, 41.2 years		

The incidence of trauma in this series was found to be lower than that recorded in most reports; a definite history of injury was obtained either before or after operation in 31 cases, or 65.9 per cent. In the other 17 cases, or 36.1 per cent, no history of even a trivial injury could be elicited despite our constant interest in this phase of the lesion. Furthermore, in the group of patients with a history of injury, the trauma was minor for exactly half of this number and might be considered major, in that consciousness was lost at the time, for the other half. Almost every type of accident has been described as giving rise to this lesion, particularly blows on the front and back of the head (Gardner [25]). It is of interest that 11 patients were injured in falls, 10 in automobile accidents and 4 in boxing; 3 accidentally bumped their heads on stationary objects. 1 was struck by a brick. 1 was kicked by a

23. Leary, T.: Subdural Hemorrhages, J. A. M. A. **103**:897 (Sept. 22) 1934.

24. Munro, D.: The Diagnosis and Treatment of Subdural Hematomata, New England J. Med. **210**:1145, 1934.

25. Gardner, W. J.: Traumatic Subdural Hematoma, Ohio State M. J. **31**:9, 1935.

horse and 1 was injured playing football. In only 2 instances was it doubtful that the trauma recorded could have been the cause of the hematoma. One patient (the patient in case 5) was injured three years before admission and at least one year before ·symptoms arose. In contrast, the patient in case 42 had a history of headaches and diplopia two months before he was rendered unconscious by an automobile accident. Among the 17 patients without a history of trauma, other possible predisposing factors, such as arteriosclerosis or alcoholism, were not of frequent occurrence. Only 2 patients had a history of alcoholism; both also had injuries. Of the 11 patients with clinical arteriosclerosis, 7 had injuries and 4 did not. It has been assumed by others that in such cases trauma has invariably occurred, although it may have been trivial and therefore forgotten by the patient. Whether or not this assumption is justified is open to question, but it would seem to be upheld by the fact that the clinical and operative findings in such cases are identical with those in cases in which there is a definite history of trauma.

Duration of Present Illness.—The present illness was of comparatively short duration in all but 2 cases. The patient in case 1 had been ill for fourteen months and was practically blind on admission. He also had been operated on elsewhere, a right subtemporal decompression having been done four months before. The patient in case 5 had a history of sick headaches for years, which were stated to have been worse for two years before admission; the time at which his other symptoms arose is not recorded. None of the other patients had symptoms of more than a year's duration. The shortest illness among the adults and minors was one week (case 36) and among the infants three days (case 44). The other infant, the child in case 9, was ill for five months. The average duration of the present illness for the entire group was thirteen weeks.

Latent Interval.—Of the 30 cases in which there was a history of trauma, a latent interval was present in only 14, or 43.3 per cent, the patients in the remaining 16 cases dating their symptoms from the time of the accident. In case 5 this period was a year (further evidence that the recorded injury was not the cause of the hematoma in this case), while in case 44 it was but four days. If these two extremes are excluded, the average length of this period was only three weeks.

Symptoms.—As noted by others, for the majority of patients with subdural hematomas the principal symptoms are those of intracranial pressure. Of the 46 adults and minors, 45, or 93.6 per cent, complained of headache, the patient in case 28 being the only exception. In but 5 cases was headache more pronounced on the side on which the hematoma occurred, while in 3 the opposite side was more affected. Headache, therefore, is of no value as a sign of localization. The next most

common complaint was drowsiness, occurring in 31 patients, or 66 per cent. Nearly the same number, 29, or 61.7 per cent, suffered from nausea or vomiting. Vertigo, apparently arising with changes in position, was recorded for 16, or 34 per cent. Only 13 patients, or 27.6 per cent, had diplopia, and 10, or 21.2 per cent, had periods of mental confusion. Weakness of one side of the body was a principal symptom for only 3 patients, or 6.3 per cent, and the same number complained of tinnitus. Convulsions occurred in 7, or 12.7 per cent. Both infants, the patients in cases 9 and 44, had generalized convulsions. Of the 5 adults, the patients in cases 29 and 34 had focal seizures and those in cases 35 and 47 and 48 had generalized convulsions. The patient in case 15 was epileptic but had no attacks during the present illness. Visual failure was complained of in 2 instances. The patient in case 1 was nearly blind with a high grade of papilledema. This was the only patient with a history of progressve deafness. The patient in case 24 was totally blind. The case of this patient was the most unusual in the series and has previously been reported by one of us (W. E. D.[26]). The visual failure and associated atrophy of the optic nerve were due to direct pressure on the optic chiasm by a hematoma surrounding the sella turcica (fig. 1). In summary, a history of symptoms possessing localizing value was obtained in but 5 cases, or 10.6 per cent (cases 8, 14, 28, 29 and 34).

Objective Findings.—For most of the patients the clinical findings were indicative of intracranial pressure only. Papilledema was present in 25, or 53.2 per cent, and absent in 21, or 44.7 per cent. Associated retinal hemorrhages occurred in 7, or 14.8 per cent. The degree of papilledema varied from less than 1 diopter to 6 diopters, with little difference on the two sides. No significant abnormalities of the visual fields were recorded. In no instance was there hemianopia. The patient in case 24, who has been mentioned, was the only patient with atrophy of the optic nerve. Central facial weakness was present in 8 cases (17 per cent), being an isolated finding in 4. Three patients (6.3 per cent) had nystagmus, and 2 (4.4 per cent) had ptosis. The patient in case 30 had bilateral ptosis, sluggish pupils and inability to look upward, while the patient in case 21 had unilateral ptosis corresponding to the side on which the hematoma was present. Anisocoria was noted in a single case (33), the larger pupil being on the same side as the hematoma. The corneal reflex was absent in 2 cases (4.4 per cent). In case 25 it corresponded to the side on which the hematoma occurred, whereas in case 37 it was also unilateral although the hematoma was bilateral. Cases 1 and 24 were the only instances of marked reduction in vision, the

26. Dandy, W. E.: The Brain: Subdural Hematoma, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 299.

patient in case 24 being blind. Of the remaining cranial nerves, none except the sixth was recorded as abnormal.

General muscular weakness was a rather frequent observation, 8 patients, or 17 per cent, being unable to stand unassisted. Weakness of the extremities on one side also occurred in 8 cases, being marked in only 2, cases 8 and 14. Interestingly, this hemiparesis occurred on the same side as the hematoma in 2 cases (cases 6 and 38). Case 31 was the only instance of hemihypesthesia. Astereognosis was not noted in a single case.
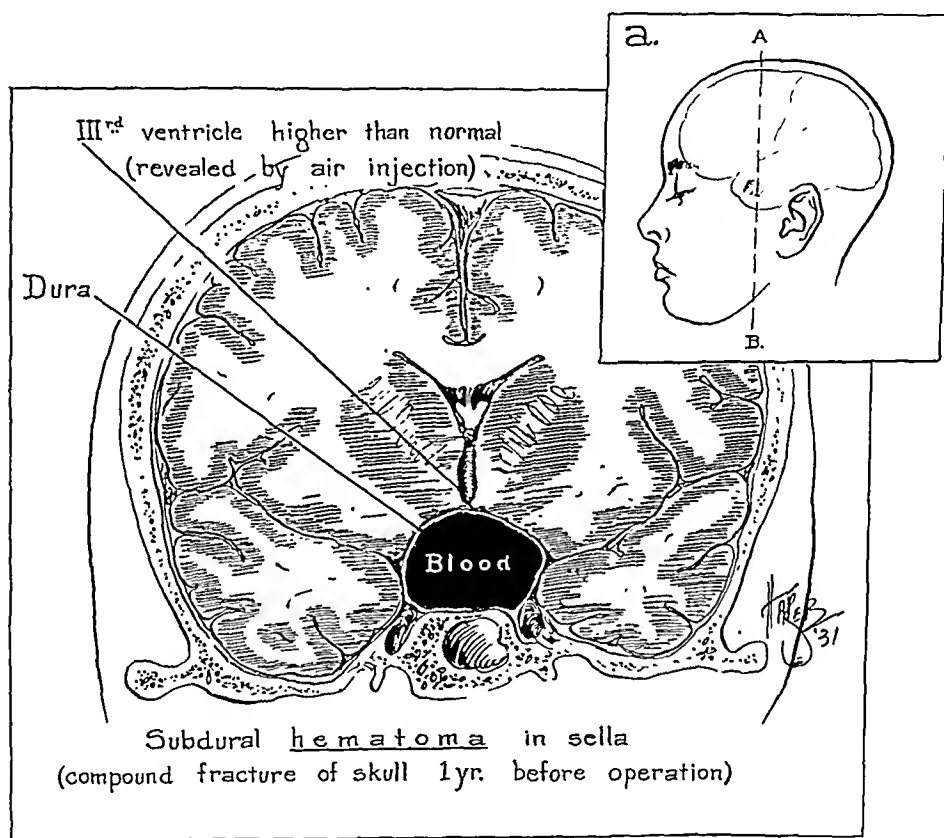
Fig. 1.—Post-traumatic subdural hematoma about the pituitary body in case 29. This patient had signs of a hypophysial tumor, including destruction of the sella turcica.

The reflexes were more frequently disturbed. The deep reflexes were bilaterally hyperactive in 9 cases, or 19.2 per cent, and unilaterally more active in 14 cases, or 30 per cent. In case 21 this hyperactivity occurred on the same side as the hematoma, while in case 17, with unilateral activity, there were bilateral hematomas. The Babinski sign was recorded in 20 cases, 44.6 per cent; it was bilaterally present in 12 cases, or 27.6 per cent, and unilaterally present in 8 cases, or 17 per cent. In cases 6 and 7 the Babinski sign occurred only on the side on

which the hematoma was present. It is significant that Fleming and Jones,[10] Frazier [15] and Kaplan [9] have noted the presence of homolateral neurologic findings, the last-named author having observed them in 5 of 8 cases. Another reflex which occurs occasionally in the presence of a tumor of the brain, namely, cervical rigidity, was observed in 3 cases (6.4 per cent).

The frequency with which a history of drowsiness was obtained has already been recorded, but it is worthy of note that 8 patients, or 17 per cent, were in coma at the time of admission and required immediate operation. Although mental confusion was recorded for 10 patients, and although a majority of the hematomas were on the left side, the patient in case 14 was the only one showing motor aphasia.

In summary, then, if one considers the reflex changes having value in the localization of the cerebral lesion and the presence of motor weakness, sensory loss and aphasia, one finds that 25 patients, or 53.2

TABLE 3.—*Symptoms in Order of Occurrence*

Symptom	Number of Cases	Percentage
Headache	44	93.6
Drowsiness	31	66
Nausea and vomiting	29	61.7
Vertigo	16	34
Diplopia	13	27.6
Mental confusion	10	21.2
Convulsions	7	12.7
Weakness on 1 side of body	3	6.3
Tinnitus	3	6.3
Failing vision	2	4.2
Failing hearing	1	2.1
Numbness of 1 side of body	1	2.1

per cent, were without positive findings, 19 patients, or 40.3 per cent, possessed them in part, and 3 patients, or 6.7 per cent, showed neurologic findings referable to the uninvolved hemisphere.

Elevation of temperature above 101 F. occurred in but 2 instances (cases 3 and 8). On the other hand, in 7 cases, or 15.5 per cent, there were leukocyte counts of more than 12,000; in cases 3, 9, 15 and 20 there was leukocytosis, the leukocyte count ranging between 15,000 and 20,000. Such a high leukocyte count is fairly common in association with subdural hydroma. Of greater significance was the pulse rate before operation. Twenty-six patients, or 55.3 per cent, had bradycardia, the pulse rate being 60 or below; 9, or 19.1 per cent, had a pulse rate between 60 and 70, and only 8, or 17 per cent, had a pulse rate above 70. In 4 cases, or 8.8 per cent, the rate was not recorded prior to operation. The only other positive physical findings of note were also in the cardiovascular system. Arteriosclerosis of the peripheral or retinal vessels was noted in 10 cases (21.2 per cent), and 10 patients had a blood pressure of 140 systolic and 90 diastolic (or higher). It is interesting that the patient in case 9, an infant, had an enlarged head

and separation of the sutures suggesting hydrocephalus. The other infant (case 43) had a head of normal size with bulging fontanels and was in coma. Both had generalized convulsions.

Most of the laboratory studies gave negative results. The Wassermann reaction of the blood was negative in every case. Lumbar punctures were done on the 2 infants, 1 of whom (case 9) had normal fluid and the other (case 43) xanthochromic fluid, apparently the most common abnormality occurring in association with this lesion. Only in case 4 did the roentgenograms show a fracture of the skull.

Clinical Diagnosis.—From what has been recorded concerning the histories of this group of patients it is not surprising that a presumptive diagnosis of subdural hematoma was made in only 12 cases, or 23.3 per cent. Twenty-nine patients, or 61.7 per cent, were thought to have a

TABLE 4.—*Neurologic Findings*

	Number of Cases	Percentage
Papilledema	25	53.2
Retinal hemorrhages	7	14.8
Atrophy of the optic nerve	1	2.2
Facial weakness (central)	8	17.0
Nystagmus	3	6.6
Ptosis	2	4.4
Anisocoria	1	2.2
Absence of corneal reflex	2	4.4
General weakness	8	17.0
Hemiparesis	8	17.0
Hemihypesthesia	1	2.2
Hyperactive deep reflexes (bilateral)	9	19.2
Unilaterally hyperactive deep reflexes	14	30.0
Bilateral Babinski sign	12	27.6
Unilateral Babinski sign	8	17.0
Cervical rigidity	3	6.4
Coma	8	17.0
Aphasia	1	2.2

tumor of the brain; 2 patients, or 4.2 per cent, were thought to have abscesses of the brain, and for a similar number the condition was diagnosed as cerebral hemorrhage. The condition of 1 patient (2.1 per cent) was diagnosed as hydrocephalus and that of 1 as arteriosclerosis of the brain. Because of the presence of blindness and atrophy of the optic nerve the patient in case 24 was believed before operation to have a tumor of the pituitary gland. Clinical differentiation between the manifestations of subdural hematoma and those of tumor of the brain is especially difficult because of the common tendency of patients to attribute their symptoms to injuries.

VENTRICULOGRAPHY

Since an unlocalized tumor of the brain is suspected in a high percentage of cases of subdural hematoma, the localization of the lesion is ultimately dependent on ventriculographic examination or its equivalent, direct puncture of the hematoma. A subdural hematoma cannot escape

detection by ventriculographic study and not infrequently the exact character of the lesion can be determined from the ventriculograms alone.

In our series of cases only the ventricular injection of air has been used. This is certain and safe, and the results are absolute. Unless there are undoubted signs of localization (and in few of these cases was this true) a surgeon will no longer take chances on finding the lesion through an operative exposure of the brain. Subdural hematomas are therefore (with only rare exceptions) localized by ventriculographic study. The spinal route for injection of air has not been used because it entails unnecessary danger and the results are capricious. In approximately one third of all spinal injections the air injected into the spinal canal will not reach the ventricular system, because the foramen of Magendie is not patent and air cannot pass through the foramens of Luschka. It is interesting in this connection that Van Dyke [27] has localized a hematoma by the subarachnoid picture of the air and regards the findings as pathognomonic.

When there is a history of recent trauma and the diagnosis of subdural hematoma is a probability or even a possibility, the openings for the ventricular puncture are regularly made anteriorly, i. e., over the anterior horns of the lateral ventricle instead of at the usual posterior site. In addition, the bony opening, instead of being made solely by a perforator, is enlarged by a burr in order that the color of the dura may be better seen and the dura may be carefully inspected as it is opened in search of a hematoma. If the dura is punctured blindly through a conical perforator opening in the bone, one may easily mistake the blood of a punctured superficial cerebral vein for that of a subdural hematoma; with a perforator opening enlarged by means of a burr, this mistake is not possible, for with such an opening one can actually see the outer membrane lining the inner surface of the dura, and if a hematoma does not exist the cortex will present. The reason for making the bony openings anteriorly is that the hematoma will usually be encountered at that point, for with occasional exceptions it extends to the midline. Frequently the hematoma ends slightly anterior to the usual site of the posterior openings, and it would be missed if the puncture were made in the occiput. There are cases in which the anterior opening also just misses a subdural hematoma. The mesial border of this lesion may be irregular, reaching the falx only in part of its course, and in one of its outward bends the dural puncture may just miss the hematoma. The only advantage in reaching a hematoma directly is the avoidance of an injection of air. If a hematoma is not

27. Van Dyke, C. H.: A Pathognomonic Encephalographic Sign of Subdural Hematoma, Bull. Neurol. Inst. New York **5**:135, 1936.

encountered the wounds are closed, and ventriculographic examination is completed in the usual fashion.

Another advantage of the anterior openings is that the occasional bilateral hematoma may be disclosed without the necessity of ventriculographic study. Moreover, in such cases it is highly probable that both lateral ventricles will be nearly or entirely obliterated by the space-occupying lesions, so that ventricular puncture is difficult or even impossible. In both of our cases in which the condition was bilateral the double lesions were disclosed solely by anterior puncture.

In 27 cases, or 57.7 per cent of the series, ventriculographic studies were made prior to operation. In 7 others, or 15.5 per cent, prepara-

TABLE 5.—*Summary of Findings in Ventriculograms from Cases of Subdural Hematoma*

Do Both Ventricles Contain Air?	Is There Contralateral Hydrocephalus	Anteroposterior View		Contralateral Ventricle Compressed	Lateral View	
		Sharp Upper Cut in Ventricle	Concavity of Outer Border		Homolateral Ventricle Reduced In Size	Filling Noted in Contralateral Ventricle
+	+ Small rounded	+	+	Slight	Entire ventricle but more in anterior horn and body	None
+	+ Slight	+ Slight	+ Slight	No	Anterior half reduced; posterior absent	+
Only contralateral	+ Slight	Not filled	Not filled	+	Ventricle obliterated	None
Only contralateral	+ Big	Not filled	Not filled	..	Ventricle obliterated	+
+	No	+	+	No	Only shred of posterior half; anterior reduced	None
+	No	+	+	No	Only slight remains	+
Only contralateral	+ Posteriorly; small anteriorly from compression	Not filled	Not filled	+	Ventricle obliterated	None

tions were made for ventriculographic examination but the hematoma was encountered when the dura was punctured en route to the ventricle. Of the total number of cases, therefore, ventriculographic examination or its equivalent was required in 75 per cent. These figures, however, do not portray the actual facts in this regard, for 5 of the cases were observed before the introduction of ventriculography in 1918. Since this time the occasion is rare indeed when ventriculographic study or its equivalent is not deemed necessary. Since 1918 these tests have been used in 64.3 per cent of cases. In 18 air was present in the third ventricle and in both lateral ventricles. In 9 cases the lateral ventricle on the side on which the hematoma was present did not contain air. In every case air reached the third ventricle, which was markedly oblique.

For several years it has been evident that the ventriculographic plates will frequently disclose a change in the ventricular system that is pathognomonic. From the ventriculograms alone, therefore, one can frequently make the diagnosis of subdural hematoma even though the history may have offered no suggestion of this lesion. To know that the intracranial lesion is a subdural hematoma and not a tumor is of the greatest importance to the operator and the patient, for the extent of the cranioplastic procedure is reduced by half and the position of the bone flap is changed.

In general it may be said that the changes demonstrable by ventriculography in cases of subdural hematoma closely resemble those in cases of dural endothelioma, which are almost but not quite pathognomonic. A dural tumor is recognized by the sharp, straight line that represents the border of the growth in the deformed ventricle. This is particularly evident in the anteroposterior view, which shows the lateral ventricle in cross section. A subdural hematoma produces a precisely similar ventricular change, i. e., a sharp, straight ventricular defect which is always on the superior surface of the affected ventricle (in cross section) ; and, in addition, it usually but not invariably induces a concave indentation on the outer surface of the lateral ventricle (in cross section). That both the superior and the outer surface of the ventricle are affected is due to the extensive distribution of the hematoma; i. e., it is both superior and lateral to the ventricle. Such a bilateral effect on the ventricle is occasionally seen with a large dural tumor, but this is infrequent. The third important ventriculographic change is seen in the lateral view. Since the hematoma usually extends from the frontal to the occipital pole, the lateral ventricle is correspondingly compressed so that the resultant ventriculographic picture shows a lateral ventricle greatly reduced in size throughout most of its horizontal extent, i. e., from the anterior horn through the body to and not infrequently including the posterior and descending horns. This again is a picture that is occasionally but uncommonly reproduced by a cerebral tumor. We have occasionally seen the aforementioned ventriculographic deformations caused by cerebral tumors surrounded by extensive cerebral edema; the findings are therefore not absolute.

The ventriculographic changes in both lateral and anteroposterior views taken in our last 9 cases are shown in the accompanying sketch (fig. 2). The pneumographic shadows have been traced from the roentgen plates. All of our earlier ventriculograms were destroyed when the inflammable roentgen plates were superseded by the modern ones that do not burn.

Ventricular changes on the side on which the lesion was present were as follows:

1. Anteroposterior view.

(*a*) In all instances there was dislocation of the ventricular system to the contralateral side.

(*b*) With one exception (*G*) the anterior horn in cross section was smaller on the side on which the lesion is present. In this instance it was about twice as large on the affected side. Why this exception
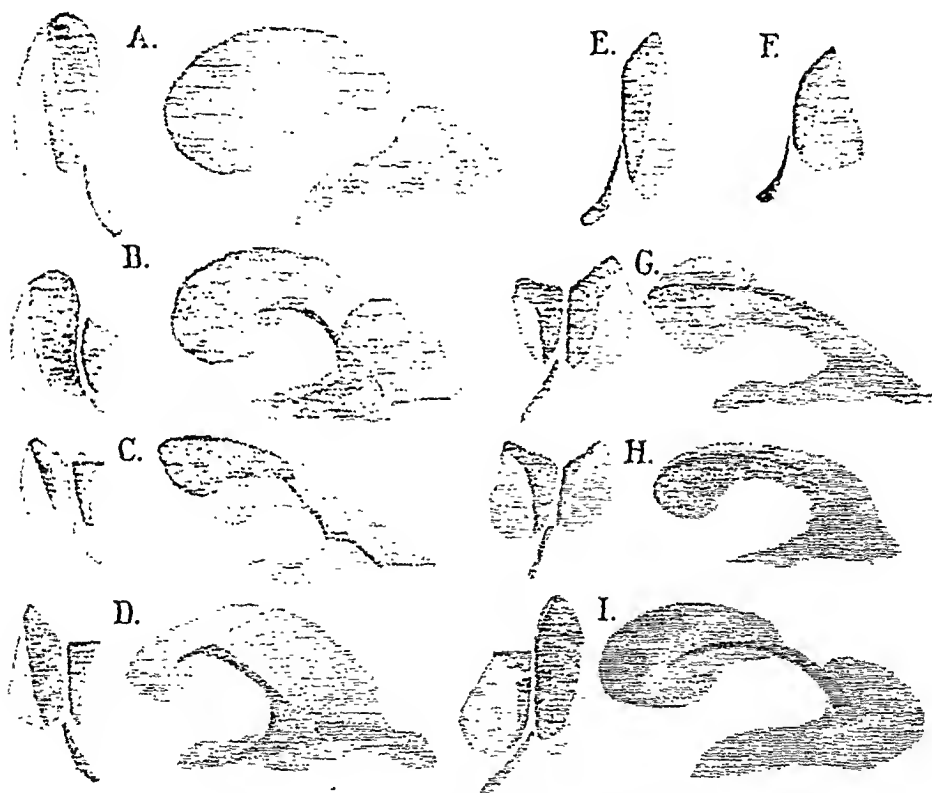
Fig. 2.—Shadows traced from ventriculograms taken in 9 cases of subdural hematoma. See text for explanation.

occurred we do not know. In the remaining cases the ventricle on the side on which the lesion was present varied in size from slightly smaller than the other to complete absence in 3 cases (*C, F,* and *I*).

(*c*) The telltale sharp upper border was present in 4 and absent in 2 of the affected ventricles that filled.

(*d*) The equally telltale concave lateral border was also present in 4 and absent in 2 of the affected ventricles that filled. The absence of these nearly pathognomonic changes in the ventricles is doubtless due to the lesser volume of the hematoma over the frontal region in these cases.

(e) The all-important obliquity of the third ventricle was well defined in every instance.

(f) In two plates the shadow of the third ventricle was strikingly club shaped (and in two others the change was present but less pronounced), rounded inferiorly and gradually flattening to an acute angle superiorly. This effect was due to the varying degree of pressure from the hematoma in the upper (greater) and the lower (lesser) end of the ventricle. It is hardly probable that this deformation has any relation to subdural hematoma.

2. Lateral view.

(a) Without exception the lateral ventricle in all cases was tremendously reduced in size throughout its longitudinal extent. The reduction in the ventricular volume may be greater in front, greater behind or essentially equal throughout. The character and extent of the reduction may be seen in fig. 2. In 3 cases (33.3 per cent) the ventricle was entirely collapsed on the affected side.

Ventricular changes on the contralateral side were as follows:

1. Hydrocephalus of varying degree was present in 6 of the 9 cases. It was advanced in 3 cases, slight in 3 and absent in 3. The cause of hydrocephalus was compression of the aqueduct of Sylvius. The lesser degree of hydrocephalus was diagnosed from the anteroposterior view when the corners of the ventricle were rounded; this is always the earliest objective evidence of ventricular dilatation. The moderate degree of hydrocephalus leads us to believe that in these cases occlusion of the aqueduct was partial and was of the ball valve type.

2. A partial filling defect about the middle of the contralateral ventricle was present in 2 cases (lateral view). This was due to the fact that the maximum volume of the hematoma compressed the opposite ventricle in this region. The greater obliquity of the third ventricle is also evidence of the great compression effect in this transverse plane.

3. Flattening of the anterior horn was definite in 2 cases (figs. 2 C and 2 I) and probably present in slight degree in a third (fig. 2 A, anteroposterior view).

PATHOLOGIC PICTURE

The striking pathologic findings in cases of subdural hematoma are:

1. A large collection of dark fluid blood is present. with a few soft brownish yellow clots dangling from the outer membrane but sometimes extending across and attached to both membranes.

2. The fluid blood when left standing in a test tube will never clot. even when normal blood is added to it: i. e.. the clotting element has been completely eliminated.

3. The blood is hermetically sealed in membranes that cannot extend; the hematoma is therefore not progressive.

4. The outer membrane is always thick (1 to 4 mm.); it is snugly attached to the dura but can be stripped from it; it is opaque and fairly vascular. Its vascularity is derived from the dura, from which new vascular channels connect with newly formed blood spaces in the membrane.

5. The inner membrane is thin, transparent and avascular. It lies loosely on the pia-arachnoid, but there is no attachment except at the margins of the hematoma, where the inner and the outer membrane are confluent; in this region there may be a firm line of attachment to the brain.

In this series the volume of the hematoma was estimated to have varied from 1.3 ounces (40 cc.) to 8 ounces (240 cc.). In case 9, 80 cc. of old blood was aspirated; in case 43, 175 cc. of fluid blood was removed from the sac, and in addition there were several fair-sized clots; in cases 46 and 47 the contents of the sac were entirely fluid and measured but 40 cc. Except for the lesions in cases 16 and 24, the hematomas were described as lying on the frontal and parietal lobes and frequently on the occipital lobe; they extended from the longitudinal sinus to the region of the sylvian vein. In 1 instance the hematoma was exclusively in the temporal region; it was directly over the site of a blow, and beneath it the brain was excavated from absorption of the contused area. In another case the hematoma was in the sella turcica, causing the sellar contents to bulge and act like a tumor. In 1 case (case 26), associated with the hematoma but separate from it was a subdural hydroma (fig. 3). In no instance have we been able to determine the source of the blood. In case 16 it seemed probable that a large thrombosed vein crossing from the atrophic defect in the temporal lobe to the dura may have been the source of the original bleeding, but there is, of course, no proof.

The condition of the blood within the membranes is of interest. That such blood no longer has power to clot is doubtless due to the extraction of the clotting substance in the formation of the outer membrane. That there remain a few small and seemingly degenerative clots within the hematoma indicates that there has originally been clot formation; it would be difficult to believe that the blood had not quickly clotted in the beginning. But why should the new tissue representing the outer membrane develop exclusively along the dura and not form throughout the volume of blood, as in Virchow's pachymeningitis interna? And why, too, should it never form on the arachnoid membrane? The fact that the dura is vascular unquestionably accounts for

the growth of vascular channels within the outer membrane, but hardly for its thickness, which is fairly uniform, or for its intrinsic character. That the inner membrane is not caused by any derivative of the blood is shown by the fact that precisely the same membrane forms in cases of subdural hydroma, in which, of course, no blood is present. One can therefore only conclude that the membrane is a product of reaction of the pia-arachnoid. It is also worthy of interest that exactly the same thin, transparent membrane is present on the dural side of a subdural hydroma, although as time advances it becomes somewhat thicker and more opaque than the inner membrane, and it too adheres tightly to the dura.
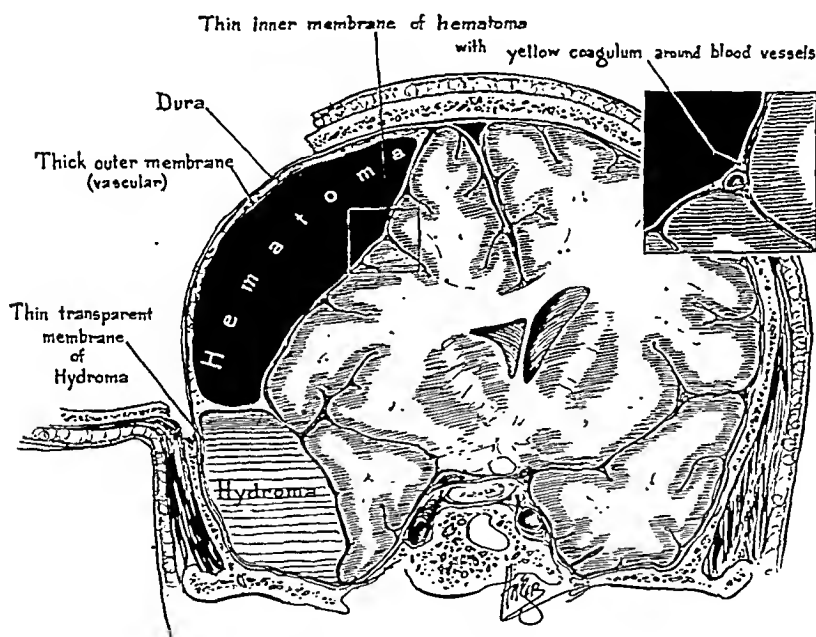
Fig. 3.—Subdural hydroma coexisting with a subdural hematoma in case 26. Both resulted from the same injury.

Can a subdural hematoma disappear spontaneously? This hardly seems possible, because the limiting membranes can scarcely absorb blood. Although vascularized, the inner surface of the outer membrane is smooth and glistening from pressure alone. We have never seen, either at operation or at necropsy, a hematoma as late as a year after its origin (except one solid clot, in case 18). This fact, together with our clinical experience, leads us to doubt that survival is possible after this time. Most of the patients that come for operation appear at a time when on account of advanced intracranial pressure the tenure of life is unquestionably short. These statements naturally lead us to doubt,

and even to deny, that Virchow's pachymeningitis is the same lesion as the subdural hematoma, even though the end result of Virchow's lesion as seen at necropsy might well lead one to assume that a large hematoma has become absorbed and replaced by fibrous tissue.

One of the most surprising findings in cases of subdural hematoma is the gross and microscopic appearance of the blood. The blood when viewed in bulk is black, but venous blood is also dark, and when the specimen is small and unless specimens of the blood from the different sources are side by side it may be difficult to tell from inspection alone that the blood is unquestionably that of a hematoma. Even when a small amount of blood from a subdural hematoma is placed on a white towel at operation and its color compared with the color of venous and arterial blood from the scalp and the dura it may be difficult to be certain that the blood from the hematoma is actually different. Usually, however, the hematomatous blood when spread on a white background is rusty brown, in contrast to the red of fresh blood. The difficulty in being absolutely certain led us to inspect the dura and the outer membranes directly through a burr opening rather than through the smaller perforator opening used for a ventricular or cerebral puncture. On one occasion a specimen of blood had been obtained through a smaller bony opening through which the dura could not be inspected. The appearance of the specimen and its color on the towel were such that a competent physician insisted that the blood was from a punctured vein; and even when the specimen was examined under a microscope most of the corpuscles were found to be well rounded or only slightly crenated—and this after being free for a period of several weeks in the cranial chamber!

Other amazing features of subdural hematoma are that it is nearly always located in the same region and that the brain almost never shows any signs of injury. Only in case 16 was the brain injured; this case presented also one of the two exceptions to the usual location, the lesion being in the temporal region. In this instance the brain was lacerated and excavated, and bridging vascular trunks crossed the defect. Except for these features the resultant hematoma was precisely similar to the remaining ones in the series. Since the hematoma almost invariably begins at the midline of the cranial chamber and spreads outward, since the outer membrane is thickest along the midline, since there are no torn veins over the surface of the brain and since the large cerebral veins are most exposed where they "jump" across from the cerebral hemisphere to the longitudinal sinus, the only conceivable explanation for a hematoma is rupture of one of these crossing veins. The bleeding would almost necessarily be into a potential cavity, and this does exist along the falx. Venous bleeding elsewhere would, with rare exceptions, be quickly stopped spontaneously by the apposi-

tion of tissues. Moreover, arterial bleeding could scarcely be responsible, for the only arteries in this region are in the substance of the brain, and the brain is practically always uninjured. Then, too, spontaneous cessation of arterial bleeding just short of severe intracranial pressure at the time would be far less probable as a consistent outcome. It might happen occasionally, but not repeatedly. One other exception to the almost uniform picture of this lesion should be noted. In 1 case (case 18) the hematoma was entirely solid and could be shelled out like a tumor and there were no membranes. In case 43 the hematoma was in large part solid.

Why this difference exists we do not know. Whether subdural hematoma uncomplicated by other factors ever causes death at once is not certain. Certainly in a high percentage of cases the danger has been little at the time and symptoms have developed a few weeks or months later. It is the progressive nature of the symptoms that has led to the widespread belief that the hematoma itself is progressive. This is, of course, precluded by the rigid and unchanging walls of the hematoma. What, then, causes the progressive symptoms and eventually death? That intracranial pressure is the cause cannot be questioned, because its relief brings immediate preservation of life. It is hardly believable that the volume of fluid blood in the hermetically sealed capsule which precludes absorption can become greater. Nor is it conceivable that new hemorrhages can occur within the rigid walls, because there are no exposed vessels that can bleed. The answer we believe to be in the reaction of the brain to the hematoma as a foreign body. We know that tremendous areas of cerebral edema surround tumors of the brain and that this occurs in variable degrees with different tumors. We also know that patients with tumors of the brain and other lesions causing intracranial pressure may be physically entirely well one minute and unconscious or dead the next from sudden strain or from a cough or even with no recognizable predisposing cause. The sudden change is due to increased cerebral edema and not to hemorrhage into the tumor. Precisely the same factors, we believe, are responsible for the gradual progression of subdural hematoma and the eventual death of the patient, i. e., the reaction in the brain from a lesion that already occupies a volume so great that the margin of security at any time is slight.

In only 3 cases was any study made of the cellular and chemical constituents of the blood. In case 26 a red blood cell count showed 5,000,000 cells per cubic centimeter. In case 43 the hemoglobin percentage (Sahli) was 103, the red blood cell count 4,100,000 per cubic centimeter and the white blood cell count 6,100 per cubic centimeter. A smear stained by the method of Wright showed the cells to be

normal in appearance but with an apparent absence of platelets. Chemical analysis showed a nonprotein nitrogen content of 28 mg. per hundred cubic centimeters, a sodium chloride content of 552 mg. and a sugar content of 40 mg. The total protein content was 5.6 mg. per hundred cubic centimeters, and the albumin-globulin ratio, 65 : 35. The hematomas that occurred in cases 46, 47 and 48, which were relatively small, measuring approximately 40 cc. each in contrast to the hematoma in case 42 measuring 175 cc., contained blood which was entirely
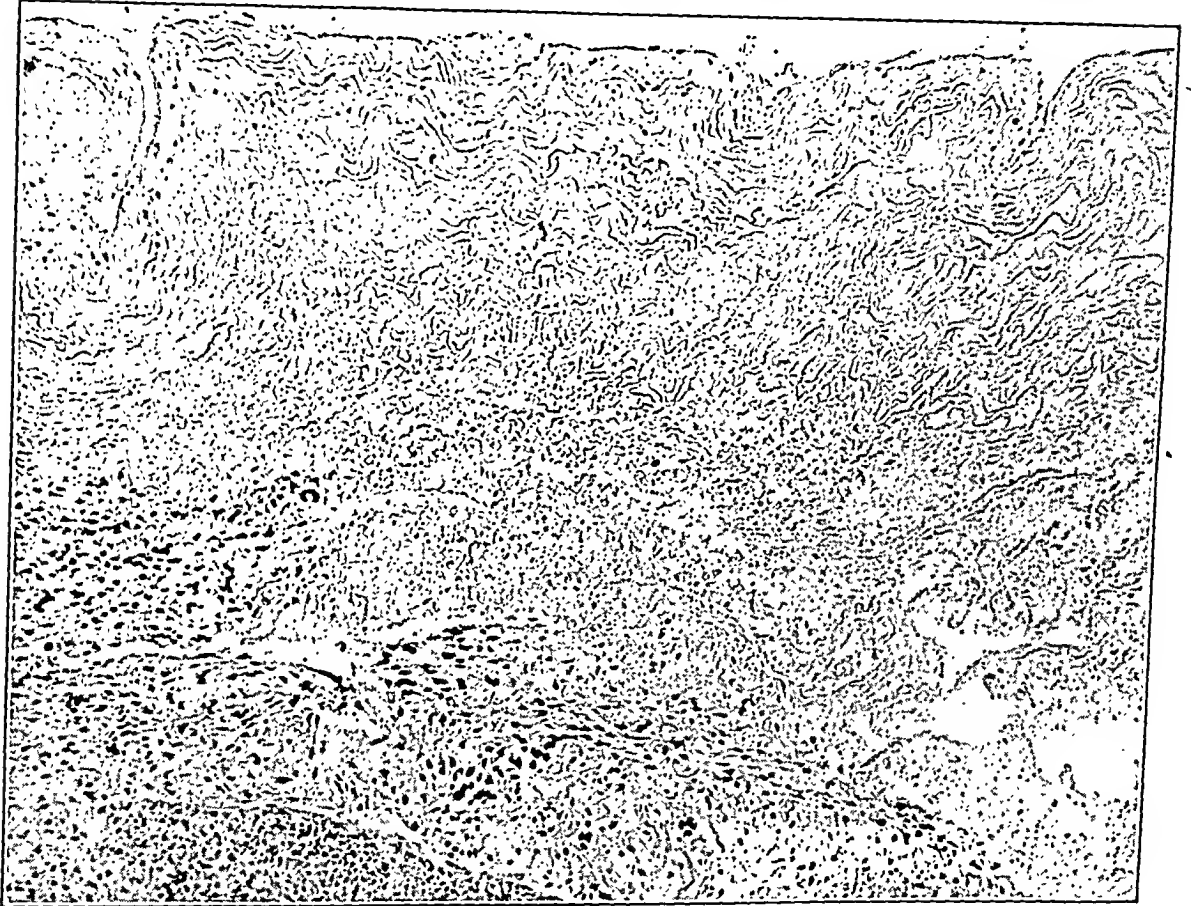
Fig. 4.—Photomicrograph of the outer membrane from the subdural hematoma in case 43. Note the relatively large number of newly developed blood vessels among the new connective tissue cells.

laked, as no red blood cells could be demonstrated in preparations. The nonprotein nitrogen content was 38 mg., and the sugar content, 25 mg., per hundred cubic centimeters. From this evidence alone the theory of gradual enlargement of the hematoma from repeated hemorrhages from the membranes, first proposed by Virchow,[2] and the more recent theory of Gardner,[12] McKenzie[11] and Zollinger,[28] that the hema-

28. Zollinger, R., and Gross, R.: Traumatic Subdural Hematoma, J. A. M. A. 103:245 (July 28) 1934.

toma enlarges by the acquisition of fluid from the subarachnoid spaces by osmosis, are both seen to be impossible. What is more probable is that, whereas the patient's symptoms are progressive, the hematoma is actually regressive after the initial period of hemorrhage. The absence of severe symptoms accompanying the original hemorrhage is probably due to the fact that it is venous and not arterial in origin. Furthermore, microscopic sections from the inner and outer membranes of the sac in all the cases in which operation was done [6] showed them to be composed of granulation tissue containing numerous capillaries, especially in the
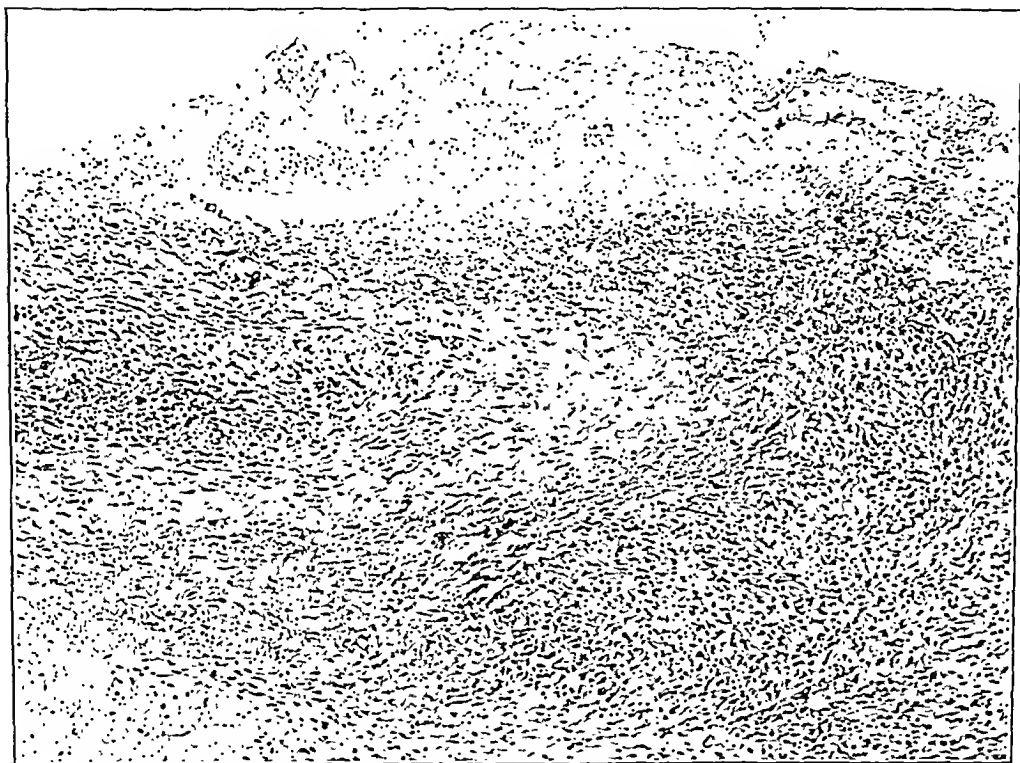
Fig. 5.—Photomicrograph of the inner membrane in case 15. The membrane shows principally a large layer of unorganized fibrin, with relatively few connective tissue cells and blood vessels.

outer membrane. Both membranes were infiltrated with leukocytes, particularly the outer membrane. There were also occasional interstitial hemorrhages (figs. 4 and 5). In no case was there evidence of any mesothelial-lined spaces as described by Cushing and Putnam.[1]

TREATMENT

Obviously the only treatment is surgical. Although repeated aspirations of a subdural hematoma have been advocated, our experience

with 1 hematoma so treated was the least satisfactory of the series; the patient recovered completely but required repeated tappings for three months. A decompression had been made, and its fulness indicated the need for the repeated relief of pressure. Our plan of attack in recent years has consistently been to turn down a very small bone flap (fig. 6), excise with the electrocautery the outer membrane flush with the dural incision and strip the thin, avascular and unattached inner membrane as far as possible from the surface of the brain. We irrigate the hematoma from the cranial chamber by flushing with Ringer's solution. Not infrequently one or more isolated pockets of blood exist
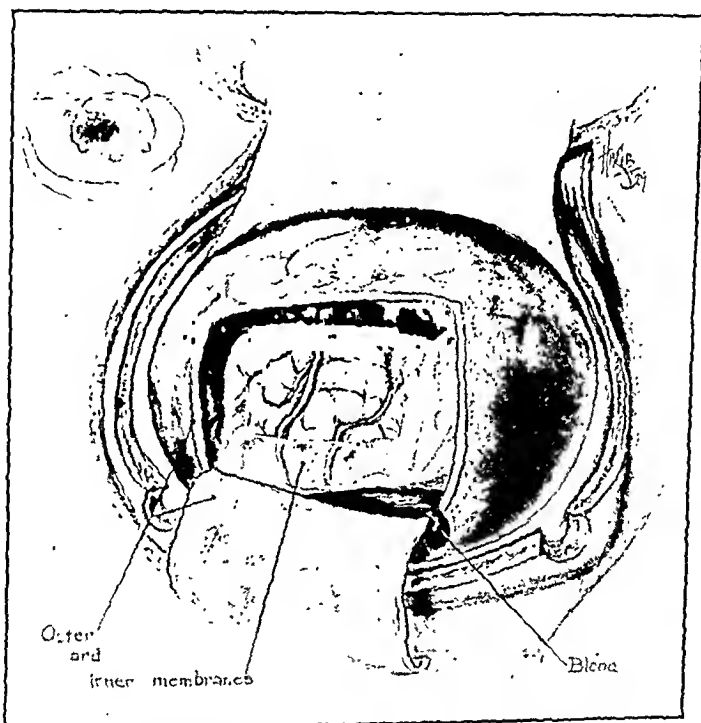
Fig. 6.—Operative view of a subdural hematoma, with windows in thicker outer membrane and thinner inner membrane. The intact brain lies beneath. Blood fills the space between the membranes. The hematoma usually covers most of the outer surface of the cerebral hemisphere.

in the subdural space. Careful inspection of this space will disclose them bulging into the large primary cavity. They are punctured, evacuated and irrigated; it has not been necessary to remove any of their covering membranes.

Whether or not removal of the inner and outer membranes is necessary cannot be stated. Since only a fraction of the entire surface area is removed and cures are unequivocal and prompt, we have gradually lessened the size of the cranial exposure and have seen no difference in the immediate or ultimate results. It is largely for this reason that the preoperative differential diagnosis of a subdural hematoma is impor-

tant. If a hematoma is still questioned after ventriculographic studies have been made, a burr opening in the line of the proposed cranial approach is inspected before the incision is made. If a hematoma is discovered in incising the dura an osteoplastic flap of approximately half the size of that necessary for a tumor will answer every purpose and correspondingly reduce the severity of the operation.

In this series the chief postoperative complication was hemorrhage, subdural or extradural or both; this occurred in 16 cases, or 34.2 per cent. In 15 of these an osteoplastic flap had been employed, and it was necessary in 2 instances to evacuate the hematoma a second time. It is interesting that on this second exposure the blood was always clotted. In case 10, in which operation was done by the subtemporal route, evacuation of the hematoma through a superimposed craniotomy opening was required. Also, the patient in case 46, with a very small hematoma, showed signs of intracranial pressure in twelve hours, owing to cerebral edema alone; he was rescued by a decompression.

The principal source of subdural postoperative bleeding is the raw edge of the outer membrane of the sac, which is fairly vascular. Bleeding from this source can now be prevented by incising the membrane by the cutting current of the electrocautery. Because of the great vascularity of the outer membrane it is important that it be not stripped from the dura beyond the dural defect, where oozing would be out of reach. Extradural bleeding is the source of greater concern than is bleeding beneath the dura. With meticulous care this can now be avoided; at least the incidence will be very low if the dura is completely incised parallel to and near the bony margins, the dura drawn tightly to the skull by several sutures and the bone largely stripped of its blood supply. Failure of the affected hemisphere to expand after operation in the absence of hemorrhage occurred in 1 case; it was overcome by placing the patient in the head-down position for twenty-four hours and by adding fluids to the circulation. Important in the postoperative care was the release of fluid and air from the subdural space by occasional tapping with a ventricular needle during the first forty-eight hours.

The danger of postoperative bleeding is scarcely less and may be even greater than that of the original hematoma; it would usually quickly end in death if not immediately recognized and promptly treated by reopening of the wound and evacuation of the clot. The detection of a postoperative hematoma requires constant and careful observation of the patient, the state of consciousness being by far the most important item. If the lesion is detected early the reopening of the wound entails no risk; if the discovery is delayed the risk increases rapidly. As most patients are very drowsy and even comatose at the time of operation, a few hours' delay in recognizing a postoperative hematoma may well cause the death of the patient. The low mortality rate in the series is

evidence of the careful study of patients by the resident surgeons. Failure to discover a postoperative hematoma is a fault scarcely to be forgiven.

The unusually high incidence of postoperative bleeding with this lesion has often led us to wonder if there may be some predisposing tendency to bleed. This probably is not so. With anesthesia induced by means of avertin with amylene hydrate there is unquestionably less bleeding, but on the other hand quite a number of these patients were operated on with the region under local anesthesia. The reduction in the size of the bone flap has unquestionably reduced both the number and the size of hematomas.
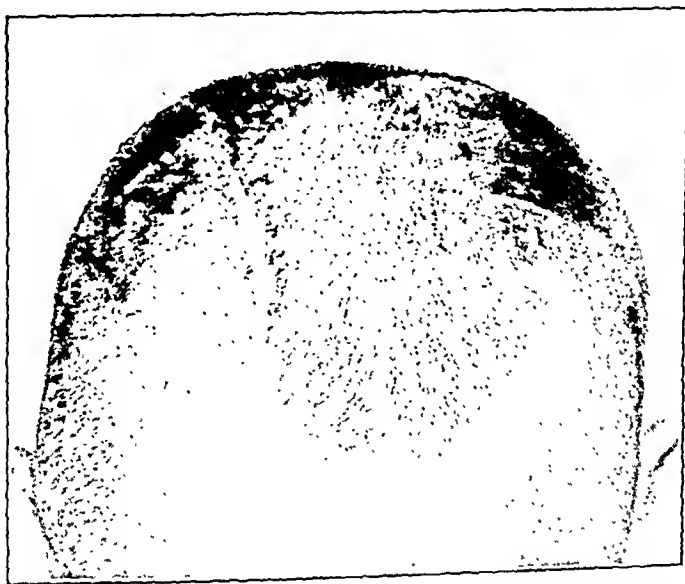
Fig. 7.—Operative scars left by surgical removal of bilateral subdural hematomas. The reduced size of the bone flap minimizes the operative risk so that both sides may be treated in a single operation.

When patients are very ill from the effects of intracranial pressure there is always the thought that it would be safer to remove the bone flap—now a small one—and play safe with life. Moreover, a postoperative hematoma would rarely form after removal of a flap. However, for cosmetic reasons, we have never done this at the primary operation because of a feeling of security as to the prompt detection of a hematoma. However, it has been necessary in several instances to remove the flap at the subsequent operation when a further risk of life was unjustifiable.

That postoperative bleeding is a serious argument against a cranioplastic operation and in favor of tapping and irrigating a hematoma cannot be denied. However, with the very low mortality in the series

the argument loses most of its force. If the patient is carefully watched there is scarcely any justification for loss of life. Then, too, when one considers the fact that the primary lesion is frequently multiple, it is clear that unless operation is performed the remaining pocket or pockets of blood may be missed, and in such circumstances a cure is scarcely to be expected. And of course tapping and irrigation offer no benefit for a patient with a solid hematoma.

Extradural drains were employed in 9 of the earlier cases (20 per cent) but were given up because of the risk of infection and because they contributed nothing to the prevention of hematoma.

When a subdural hematoma is present on both sides, the patient is placed in the so-called cerebellar position and the same procedure carried out on each side. Since the reduced size of the bone flap has cut the operative risk proportionately, both sides can be operated on with a single procedure (fig. 7).

RESULTS

Among the 48 patients there were 50 hematomas, the lesions of 2 patients being bilateral. Forty-six patients recovered and 2 died. The patient mortality therefore is 4.1 per cent; the case mortality, 4 per cent. The patient in case 27 had a wound infection and died of staphylococcic meningitis on the tenth day after the operation. Autopsy showed no other pathologic change. The patient in case 7 was in coma, with a temperature of 103.6 F., at the time of operation and died two days later. Autopsy in this case revealed nothing except edema of the brain. At the time of discharge from the hospital all the other patients were well. Subsequent reports from this group of patients have been gratifying. Twenty-eight are known to be in normal health in 1937, and among these are 2 who were operated on twenty years ago. No replies were received from 12 patients, and 6 are known to have died from causes unrelated to the hematoma a considerable time after their discharge from the hospital.

In summary, then, from this review of 48 cases one may conclude:

1. Subdural hematoma occurs with almost equal frequency in every decade of life.

2. Whereas trauma is probably the immediate cause of the hemorrhage, there may be some additional but unrecognized factor.

3. After the initial hemorrhage there can scarcely be any increase in size of the hematoma.

4. The diagnosis is difficult because unless the history of trauma is acceptable the clinical symptoms and findings do not differ from those produced by any intracranial space-occupying lesion.

5. In the cases in which trephining does not disclose the hematoma, adequate and at times precise localization can be made by ventriculographic study.

6. When a hematoma is suspected but not proved, a burr opening is made over the parietal region. Incision of the dura will establish or eliminate the diagnosis and determine the size and position of the bone flap.

7. A small craniotomy opening with evacuation of the hematoma is the operation of choice.

8. Postoperative bleeding has been of frequent occurrence. For very ill patients a decompression may occasionally be essential to recovery.

SURGICAL TREATMENT OF DIABETES MELLITUS

BILATERAL SECTION OF THE SPLANCHNIC NERVE
AND DENERVATION OF THE LIVER

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In a communication before the Twelfth Congress of Physiology at Stockholm, Sweden, and in many subsequent papers, the Hungarian pharmacologist Mansfeld reported that he had observed a decrease of the blood sugar level after massive ligature of a part of the pancreas in which the circulation in the blood vessels was maintained. The decrease was more marked after two to three days of fasting (*Karenz-hypoglykämie*), and blood sugar curves after administration of dextrose indicated a better carbohydrate tolerance. On the basis of these findings, Linhardt and Hüttl [1] performed the operation in man with satisfactory results, which were later confirmed by de Takáts [2] and Wilder, who isolated with the thermocautery a piece of the pancreas of a 13 year old boy.

Thus the idea of a surgical cure of diabetes mellitus arose and gradually made progress. Returning to the argument today, I am sorry to say that the theoretic conceptions of the Hungarian pharmacologist have not led to any practical success. Opposition soon arose in the experimental field on the part of Ljvraga, Nather, Priesel and Wagner, Caccuri, Wohlgemuth, Seo and Mochizuki, Perrotti, Gahler, Ladurner and Unterrichter, Demel and Krammer and Falin,[3] who were

1. Hüttl, T.: Versuche zur operativen Therapie des Diabetes, Orvósképzés **24**:7, 1934; Versuche zur operativen Behandlung der Zuckerkrankheit, Beitr. z. klin. Chir. **163**:206, 1936.

2. de Takáts, G.: Die chirurgische Beeinflussung des jugendlichen Diabetes, Arch. f. klin. Chir. **177**:242, 1933; Chirurgische Massnahmen zur Hebung der Zuckertoleranz, Klin. Wchnschr. **12**:623, 1933; Splanchnic Nerve Section in Juvenile Diabetes: II. Technic and Postoperative Management, Ann. Surg. **102**:22, 1935.

3. Falin, L.: Langerhanssche Inseln und Blutzucker nach Unterbindung der Ausführungsgänge der Bauchspeicheldrüse, Virchows Arch. f. path. Anat. **284**: 713, 1932.

followed in the clinical field by Pieri,[4] Hüttl and de Takáts,[2] who in a later paper recognized the error of the method he had previously followed.

This is fully justified by the results I have already published.[5] I stated that:

1. The isolation by ligature in mass of a part of a dog's pancreas from the duodenum, performed in such a manner that the connections through the blood vessels are maintained but pancreatic juice from the ligated part cannot flow into the intestine, is an operation which is well tolerated if of limited extent but poorly so if it is extensive.

2. Such an operation causes, after a while, atrophy of the acinous tissue, with a more marked sclerosis of the ligated tract, until it is reduced to a small cord of compact connective tissue, in which, however, the ganglions of the nerves and the pacinian corpuscles (in the cat) are conserved, a fact which proves the persistence of the blood supply. The islands of Langerhans do not show any special resistance, but they share the lot of the exocrine part of the organ, which sometimes presents involutional aspects resembling insular tissue.[6]

3. In the animal on which the operation is performed, the sugar content of the blood after a fast of twenty-four hours is much lower than in normal animals; after two to three days of fasting it becomes still lower. The increase in the sugar content of the blood after 1.75 Gm. of dextrose per kilogram of body weight has been given is usually less marked if the dextrose is given after not more than twenty-four hours of fasting, but it lasts longer, although it is often less marked, if the dextrose is given after two to three days of fasting. Only traces of insulin eliminated through the kidneys are found in the urine collected six to twelve hours after the last meal; insulin disappears completely after two to three days of fasting.

4. The character of the feces of the animals submitted to this operation, their loss of weight if adult and their failure to change in weight if young are signs of functional insufficiency of the external secretion of the ligated part of the pancreas.

5. The alterations which have been mentioned in the sugar content of the blood after fasting and after the carbohydrate tolerance test, the decrease and even disappearance of glycogen in the liver and the lower urinary elimination of insulin are proofs of functional insuf-

4. Pieri: Tentativi di cura chirurgica del diabete pancreatico, Soc. med.-chir. Bellunese, 1933, vol. 3.

5. Ljvraga, P.: 'Effetti della legatura massiva di una parte del pancreas, Arch. d. Ist. biochim. ital. **3**:391, 1931.

6. Ljvraga, P.: Innere und aüssere Sekretion der Drüsen, Arch. f. exper. Path. u. Pharmakol. **175**:572, 1934.

ficiency of the islands in the ligated part of the pancreas; therefore, there is a less active synthesis of glycogen from dextrose, while the opposite reaction is accelerated.

6. The suggestion by some authors of the ligature of a piece of the pancreas as a surgical treatment for diabetes does not seem to have any experimental basis, according to the data cited in this paper.

With the intention of furnishing the diseased organism a new tissue which would be able to function continuously and in harmony with the synergic organs, the so-called modified, sclerotic, atrophic or insular pancreas has been used in grafts. This modified organ was tested in animals by Jorns and Brancati. It is well known that the pancreas is particularly unsuitable for grafts, as it causes necrosis of the subcutaneous fatty tissue and necrobiosis of the adjoining tissues in other sites (Alessandri, Ottolenghi, Fichera). These modified glandular grafts seemed to have some real advantages. Unfortunately, even after seven to twelve months with completely fibrous organs some almost unimpaired lobules are not infrequently found (Ljvraga, Testa). After this lapse of time, if the complete harmlessness of the graft is to be assured, the insular tissue also must have been influenced by the newly created conditions to the extent that of the insular condition it retains only the name and the distribution in the midst of the intense sclerosis (Pende, Tiberti, Ukai, Wohlgemuth, Seo and Mochizuki, Caccuri, Ljvraga). It is then obvious that, even if this condition proves the atrophy of the ferment-producing tissue, on the other hand it hinders the nutritional exchanges between the graft and the surrounding tissues, thereby rendering difficult the setting of the transplant. In fact, it must be noticed that these grafts of modified pancreas have not had great success.

Experiments tending to find a basis for the surgical cure of diabetes were later performed by Goljanitzki, who studied in dogs the effects of the ligature of Stensen's duct on the sugar content of the blood and, encouraged by his results, together with Smirnowa [7] performed this operation on human subjects. In this procedure he was followed by Neuber, advised by Mansfeld, by Gohrbrandt, at the request of Seelig, [8] and by Angyan, Lucherini and Sussi. It may be stated, however, that the results were far from excellent.

In this connection, it may be said that I have been led into opposition to Goljanitzki, Parhon and Cahane, Urechia, Ciocanelli and Retezeanu, Dobrzaniecki and Michalowsky and Asano [9] by my experimental

7. Goljanitzki and Smirnowa: Weitere Erfahrungen mit der chirurgischen Behandlung des Diabetes, Ztschr. f. klin. Med. **105**:661, 1927.

8. Seelig, S.: Zur chirurgischen Behandlung der Zuckerkrankheit, Arch. f. klin. Chir. **157**:322, 1929.

9. Asano, Y.: Ueber die endokrine Funktion der Speicheldrüsen, Arch. f. jap. Chir. **12**:155, 213, 255 and 298, 1935.

controls of the histologic observations and by biochemical research on the salivary glands. Ligature of the salivary ducts or denervation or extirpation of the salivary glands, associated or not with partial or total pancreatectomy, led me to consider unfounded the view that there is an internal secretion, the study of which may have practical results leading to a surgical cure for diabetes. This opinion was later confirmed by the publications of Docimo.[10] Palma,[11] Glaser and Bannet,[12] Nishiyama,[13] Zimmerman and Soskin [14] and Simonetta.[14a]

All surgical intervention which tended toward hormonal substitution as a cure for diabetes having proved unsuccessful, another series of surgical corrections from a hormonal standpoint was attempted; based on present knowledge of the relations between the pancreas and other antagonistic glands, the thyroid, pituitary and adrenal, according to the well known table by Eppinger, Falta and Rudinger.

Friedmann and Gottesmann studied the effects of the ligature of the thyroid arteries; Allen studied the effects of the more or less extensive ablation of the gland. Rudy, Blumgart and Berlin (1935)[15] observed clinically the advantages of thyroidectomy in diabetes; Wilder, Foster and Pemberton (1934)[16] noted an improvement coincident with the appearance of a myxedematous condition. The administration of thyroid caused a return to the previous condition.

As to the pituitary gland, Houssay, Biasotti and co-workers had stated that in dogs deprived of it the extirpation of the pancreas does not cause a rise in the sugar content of the blood or dextrose in the

10. Docimo, L.: Gli effetti della legatura dei dotti di Stenone e della irradiazione della parotide sul metabolismo idrocarbonato, Gior. di clin. med. **14:** 510, 1933.

11. Palma, R.: Legatura dei dotti di Stenone e asportazione del pancreas, Riv. di pat. sper. **6:**419, 1931.

12. Glaser, E., and Bannet, I.: Wirken die Speicheldrüsen auf den Kohlehydratstoffwechsel inkretorisch ein? Klin. Wchnschr. **12:**345, 1933.

. 13. Nishiyama, Y.: Beitrag zur Kenntnis der Entwicklung der Glandula submaxillaris beim Kaninchen, nebst Bemerkungen über die Entstehung der sogenannten Bermann'schen Drüsen, Keijo J. Med. **3:**74, 1932.

14. Zimmerman, L. M.: Effect of Ligation of the Parotid Ducts on the Carbohydrate Tolerance of Normal Dogs, Arch. Int. Med. **49:**409 (March) 1932. Zimmerman, L. M., and Soskin, S.: Effect of Ligation of the Parotid Duct on the Carbohydrate Metabolism of Totally Depancreatized Dogs, ibid. **49:**663 (April) 1932.

14a. Simonetta, B.: Lo stato attuale delle nostre conoscenze intorno alla supposta secrezione interna delle ghiandole salivari, Athena **7:**74, 1938.

15. Rudy, A.; Blumgart, H. L., and Berlin, D. D.: Carbohydrate Metabolism in Human Hypothyroidism Induced by Total Thyroidectomy: III. A Case of Diabetes Mellitus Treated by Total Ablation of the Normal Thyroid Gland, Am. J. M. Sc. **190:**51, 1935.

16. Wilder, R. M.; Foster, R. F., and Pemberton, J. de J.: Total Thyroidectomy in Diabetes Mellitus, Endocrinology **18:**455, 1934.

urine.   Davis [17] in his experimental research confirmed the findings of the South American authors.   Considering the possibility of nervous influences—let me mention the *diabète tubérien* of Camus, Gournay and Le Grand (1925) [18]—Davis proved that if lesions are induced by the Horsley-Clarke apparatus in two localized symmetric points on the sides of the tuber cinereum, a little laterally with respect to the mamillary bodies, pancreatectomy will not cause diabetes.   Chabanier, Puech, Lobo-Onell and Lélu [19] related some success in treating a diabetic condition in a 31 year old woman by the extirpation of the anterior lobe of the normal hypophysis.   Thus they confirmed the results obtained by Hutton and Merle with the irradiation of the gland.

The. adrenals also have been the object of surgical intervention in the treatment of diabetes in man.   Ciminata,[20] in Baglioni's physiologic department, noticed that after bilateral denervation of the adrenals stimulation of the sciatic and other nerves with induced electric currents does not modify the sugar content of the blood or gives only a slight increase.   He therefore stated that the intervention interrupts the reflex arc through which the increase in the sugar content of the blood is produced by means of epinephrine.   The epinephrine contained in the denervated adrenals of cats deprived of the brain and spinal cord is less than normal, an observation which supports the statements of Tscheboksaroff, Stewart and Rogoff.[21]   Ciminata deduced the possibility of influencing in this manner the sugar content of the blood in animals with experimental diabetes.   The results of experiment confirmed this view and moreover proved that a positive adrenal factor is associated with a negative pancreatic factor, as Zuelzer had suggested.

The first denervation of the adrenals for human diabetes was performed by Donati in 1929.[22]   The patient, a 57 year old woman, six

17. Davis, L.:   The Relation of the Hypophysis. Hypothalamus and the Autonomic Nervous System to the Carbohydrate Metabolism. Ann. Surg. **100:** 654, 1934.

18. Camus, J.; Gournay. J. J.. and Le Grand, A.: Diabète sucré par lésion nerveuse. Presse méd. **33:**249, 1925.

19. Chabanier, H.; Puech. P.: Lobo-Onell, C., and Lélu. E.: Hypophyse et diabète (à propos de l'ablation d'une hypophyse normale dans un cas de diabète grave), Presse méd. **44:**986. 1936.

20. Ciminata, A.: Guarigione del diabete pancreatico sperimentale, con l'enervazione operatoria delle glandule surrenali, Arch. di pat. e clin. med. **8:** 79, 1929.

21. Rogoff, J. M.: Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus, J. A. M. A. **106:**279 (Jan. 25) 1936.

22. Donati. M.: Le problème du diabète au pointe de vue chirurgical. Lyon chir. **31:**133, 1934; Tentativo di trattamento chirurgico del diabete con la enervazione di una capsula surrenale. Gior. d. r. Accad. di med. di Torino **92:** 463, 1929.

months before the operation had noted the first symptoms of fairly severe diabetes. The intervention, by means of a dorsolumbar incision, was unilateral (left) and was followed by marked improvement, which, however, was found three years later not to have persisted completely. Similar cases have been reported by Corachan and Simarro (1930) [23] and by Schmidt (1932). Finally Giordano [24] performed the denervation bilaterally, with two separate interventions, one on each side, in 2 diabetic patients with favorable results on the metabolism of carbohydrates. The diabetic gangrene presented by 1 of the patients, however, was not influenced. Therefore, the opinion expressed by Oppel, that unilateral adrenalectomy should be used preferably in cases of diabetes with gangrene of the extremities does not seem acceptable. Experimental controls on animals, however, proved that this intervention was unable to modify the course of apancreatic diabetes (Catan and Mazzocco, Turcatti, Viale, Carrasco Formiguera and Puche,[25] Hill and Koehler,[26] Labois and Ljvraga).

As the conclusion of my research, it was stated that acute diabetes caused by total pancreatectomy and milder forms caused by partial pancreatectomy were not favorably influenced by any intervention tending to diminish the secretion of epinephrine. Moreover, it was stated, in agreement with Pende, that denervation of the adrenals leads to complete atrophy of the medullary part, of which there remains a knot of substituted connective tissue, full of chalky depositions. Similar results were observed after the medullary part of the adrenals was removed with a sharp curet. Other authors have confirmed my conclusions; among them are de Takáts [2] and Gondard,[27] the latter from the institute of physiology directed by Hédon, who agrees with Nothmann in stating that Ciminata's results are to be attributed to imperfection in his method of extirpating the adrenals.

Perotti and Caprì,[28] deeming that the denervation of the adrenals is a difficult intervention to execute in man, studied the effects of partial

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23. Corachan, M.: *L'énervation des surrénals dans le traitement du diabéte,* Trav. et mém. Cong. Soc. franç. chir., 1934, p. 898. Corachan, M., and Simarro, · J.: Un caso de diabetes mellitus tratado con resultado favorable par la enervación operatoria de una glándula suprarrenal, Rev. méd. de Barcelona **14:**114, 1930; Arch. franco-belges de chir., 1934, p. 901.

24. Giordano: Deficienze circolatorie e gangrene dei piedi, Rassegna clin sc. **1:**403, 1933.

25. Carrasco Formiguera, R., and Puche, J.: Enervation des surrénales et diabète expérimental, Compt. rend. Soc. de biol. **108:**27 and 171, 1931.

26. Hill, E., and Koehler, A. E.: Effect of Suprarenalectomy on Sugar Tolerance, Proc. Soc. Exper. Biol. & Med. **30:**244, 1932.

27. Gondard, L.: Diabète et capsules surrénales. Résultats expérimentaux de la suppression de l'activité médullaire, Arch. internat. de physiol. **36:**329, 1933.

28. Caprì: Comportamento del diabete sperimentale dopo surrenectomia parziale, Boll. Soc. ital. di biol. sper. **8:**436, 1933.

adrenalectomy on the course of apancreatic diabetes. A series of unilateral adrenalectomies, which had been performed in man for various therapeutic reasons, showed that the intervention is well tolerated, the remaining adrenal having proved itself able to assume the function of both. The moderate improvement obtained was, however, temporary, as was to be expected, the effects of the intervention being nullified by the hyperplasia of the remaining adrenal tissue. On the other hand, Racchiusa and Criserà observed that in dogs from which the medullary adrenal tissue and in some cases most of the cortical tissue also had been removed not only was there no lowering of the sugar content of the blood but in several cases there was a tendency toward hyperglycemia as shown by the dextrose tolerance test.

In man too, Sussig brought about no improvement by intervention of this type in a case of diabetes in a child in which ligature of the salivary (Stensen's) duct had previously been performed without noticeable results. Pieri,[4] having observed that after extirpation of the left adrenal gland in a case of hypertension the blood sugar diminished, was led to perform the same intervention in a 23 year old diabetic patient. This case is of little value as evidence, however, since the patient died five months later.

The sympathetic nervous system also has been the object of much research in attempts to find a practical surgical cure for diabetes. Rupp observed hypersensibility to insulin after section of the splanchnic nerves, and Stelling observed a diminution in the sugar content of the blood for some hours after anesthesia of these nerves in 77 per cent of his cases of diabetes. These results led de Takáts and Cuthbert[29] to study the effects of bilateral splanchnicotomy on the sugar content of the blood in dogs. These authors observed a better carbohydrate tolerance, a phenomenon which had likewise been observed after denervation of the adrenals. Subsequently de Takáts and his co-workers Fenn and Trump[30] performed splanchnicotomy in man by a method similar to that described by Pieri,[4] who stressed that this intervention should be applied in cases of diabetes in children who are resistant to insulin and sensitive to ergotamine. The operation, performed on a 13 year old girl, lowered the daily requirement of insulin from 40 to 20 units. The authors concluded that the girl remained diabetic as before, although more sensitive toward insulin; this conclusion does not seem encouraging. Nevertheless, de Takáts affirmed, not without reason,

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29. de Takáts, G., and Cuthbert, E. P.: Effect of Suprarenal Denervation and Splanchnic Section on the Sugar Tolerance of Dogs, Arch. Surg. **30**:151 (Jan.) 1935.

30. de Takáts, G., and Fenn, G. K.: Bilateral Splanchnic Nerve Section in a Juvenile Diabetic, Ann. Int. Med. **7**:422, 1933. de Takáts, G.; Fenn, G. K., and Trump, R. A.: Splanchnic Nerve Section in Juvenile Diabetes: I. Selection of Cases for Operation, Ann. Int. Med. **7**:1201, 1934.

that apancreatic diabetes in dogs is only partially comparable to human diabetes and that the intervention should be attempted only in the treatment of diabetes in children, which represents the genuine form of the disease, and he stressed the importance of this intervention. He moreover reported other cases, in 1 of which the daily requirement of insulin was reduced from 50 to 5 units.

Donati, before the Society of Surgery of Lombardy (Italy), reported a splanchnicectomy on the left side (Pende's operation) in a case of hypertension (nondiabetic) after which no changes in the sugar content of the blood were noted. On the other hand, Stropeni [31] reported that in 1 of 2 cases of angiotrophoneurosis treated by cutting the splanchnic nerves the blood sugar diminished from 130 to 90 mg. per hundred cubic centimeters. Ciceri and Gabrielli [32] performed anesthesia or alcoholic treatment of the splanchnic nerves in both diabetic and nondiabetic persons; besides a fall in the blood pressure, they observed an early, rapid and marked drop in the blood sugar curve, indicating better carbohydrate tolerance.

In the experimental field Puche reported that he noted no decrease in the blood sugar after splanchnicotomy in normal dogs. De Takáts [33] studied also the effects of the extirpation of the celiac ganglion in animals. He stated that this intervention brings about a marked increase in carbohydrate tolerance and hypersensibility to insulin. Apparently he had not taken into consideration the effects, observed by Marassini and many others, that such an intervention has on the abdominal organs. Spadolini recently called attention to the dangers of such an operation. Other authors turned their attention toward one of the organs more directly concerned with the metabolism of carbohydrates, the liver, the capital importance of which was proved by C. Bernard's studies on glycogenesis and received new light from Mann and Magth's experiments in hepatectomy.

Depisch, Hasenöhrl and Schönbauer,[34] of Falta's school, performed the denervation of the hilus of the liver in normal animals and in ani-

31. Stropeni, L.: La sezione dei nervi splancnici (operazione di Pende) nella cura della arteriopatie spastiche, Boll. e mem. Soc. piemontese di chir. 4:1184, 1934.

32. Ciceri, C., and Gabrielli, S.: Effetti immediati e lontani sulla curva glicemica e sulla pressione arteriosa della enervazione monolaterale e bilaterale delle surrenali, Ann. ital. di chir. 13:417, 1934; Studi sulle variazioni della glicemia alimentare indotte dalla alcoolizzazione degli splancnici: Tentativi di cura del diabete mellito, ibid. 38:121, 1934.

33. de Takáts, G., and Cuthbert, F. P.: Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, Am. J. Physiol. 102:614, 1932.

34. Depisch, F.; Hasenöhrl, R., and Schönbauer, L.: (a) Ueber die operative Beeinflussung des Zuckerstoffwechsels; die Durchsneidung der vegetativen Nerven im ligamentum hepatoduodenale beim normalen Hund, Klin. Wchnschr. 9:1437, 1930; (b) Wien. klin. Wchnschr. 43:125, 1930.

mals with mild experimental diabetes; a marked decrease in the blood sugar curves after administration of dextrose was observed, indicating a better carbohydrate tolerance. In 1 dog, however, with severe diabetes from subtotal ablation of the pancreas, no favorable influence was exerted by the intervention. It must be recalled here that Christie, Macleod and Pearce [35] had previously reported observing after stimulation of the hepatic plexus effects similar to those produced by puncture of the fourth ventricle. Kaufmann, however, sustained the view that total denervation of the liver does not modify the regulation of blood sugar in animals deprived of the pancreas, although it lowers the blood sugar in normal animals. Leone [36] observed a temporary alteration in the biligenic and glycogenic functions of the liver in dogs after sympathectomy of the hepatic artery. Chianello [37] reported after the same intervention a considerable congestion of the liver and a constant and gradual decrease in the sugar content of the blood during a period of thirty to fifty-six days, after which time the circulation of the blood was restored. On the contrary, sympathectomy of the portal vein caused the blood sugar to increase definitely for one month and then to fall below the preoperative level.

De Fermo [38] reported low blood sugar readings with the lowest between the tenth and the twentieth day after intervention, and a lowering of the dextrose tolerance curves for a period of one to two months. Komatsu [39] reported a better tolerance of carbohydrates introduced per os after sectioning all the nerve filaments contained in the hepatoduodenal ligament. The higher apex and the later return to the initial readings of the dextrose tolerance curve after partial extirpation of the pancreas fell to normal or nearly normal readings after denervation of the liver. Denervation was performed from two and a half to four months after the first intervention in cases of rather mild diabetic conditions (one eighth to one fourth of the pancreas left). The denervation of the liver associated with simultaneous partial pancreatectomy.

35. Macleod. J. J. R., and Pearce. R. G.: The Relationship of the Adrenal Glands to Sugar Production by the Liver, Am. J. Physiol. 29:419, 1911-1912.

36. Leone, P.: La simpaticectomia dell'arteria epatica in rapporto ai processi riparativi ed alle funzione biligenica e glicogenica del fegato, Arch. ital. di chir. 18:346, 1927.

37. Chianello, C.: La simpatectomia della vena porta, Ann. ital. di chir. 9: 343, 1930; Modificazioni istologiche del fegato ed influenza sulla glicemia in seguito alla simpaticectomia dell' arteria epatica, Cultura med. mod. 6:411, 1927; La simpatectomia dell' arteria epatica, ibid. 8:289, 1929.

38. de Fermo, C.: Studi sperimentali sulla simpaticectomia perivasale. Esame funzionale del fegato nella simpaticectomia dell'arteria epatica, Arch. ital. di chir. 28:381, 1931.

39. Komatsu, Y.: Ueber die operative Beeinflussung des Zuckerstoffwechsels. Arch. f. klin. Chir. 174:65, 1932.

even with mild diabetes, was followed by a smaller increase in the blood sugar after administration of dextrose and by a more noticeable hypoglycemia after meals. Epinephrine, which usually causes a greater increase in the blood sugar in diabetic dogs than in normal dogs, caused no variations in either group.

Donald [40] and de Takáts,[29] on the other hand, observed no influence from denervation of the liver on the carbohydrate tolerance. This agrees with Kaufmann's findings, already mentioned, and with those cited by Palmer [41] in his monograph on hepatolytic intoxication. In the clinical field, Hirschhorn and Popper [42] observed after paravertebral anesthetic block of the eighth, ninth and tenth right dorsal nerves a smaller increase of the blood sugar after meals, hypersensibility to insulin and absence of the increase of the blood sugar caused by epinephrine. The blood sugar, which remained unchanged in normal persons, was often markedly lowered in persons with diabetes. Finally, let me mention the experimental work with ergotamine done by Moretti, Bufano, Cesa-Bianchi, Franco, Pollak and Selinger, Rothlin and others. These authors observed in diabetic patients that this drug, alone or associated with atropine, lowered the sugar content of the blood.

EXPERIMENTS IN SPLANCHNICOTOMY AND DENERVATION OF THE HILUS OF THE LIVER

After the series of experiments I had already undertaken for the purpose of studying the possibility of a surgical cure for diabetes, which I have mentioned, I undertook a complementary study of the effects of splanchnicotomy and denervation of the hilus of the liver on the blood sugar in normal animals and in animals with experimental diabetes. The former of these interventions has been performed on man because of various clinical indications (by Durante,[43] Craig and Brown, Donati,[22] Pieri,[4] Stropeni [31] and others), and the latter seemed to me an intervention which would not be difficult to apply clinically.

For the determination of the blood sugar I used the Folin-Wu method. This method gives slightly higher figures than the Bang and the Hagedorn-Jensen method, but it has been preferred in laboratory

40. Donald, J. M.: Studies on Carbohydrate Metabolism Following Denervation of the Liver, Am. J. Physiol. **98**:605, 1931.

41. Palmer, R. G.: Physiopathologie des opérations sur le foie et les vaisseux hépatiques, Paris, E. Le François, 1934.

42. Hirschhorn, S., and Popper, H. L.: Ueber den Einfluss der paravertebralen Injektion auf Vorgänge der Stoffwechselregulation, Wien. klin. Wchnschr. **46**:365, 1933. Popper, H. L., and Hirschhorn, S.: Die Beeinflussung der Galaktoseausscheidung durch paravertebrale Injektion, ibid. **45**:268, 1932.

43. Durante, L.: La midollectomia surrenale isolata ed associata alla resezione dei nervi splancnici, J. internat. de chir. **1**:579, 1936.

tests because of the greater constancy of the results for comparative purposes. The animals used were 18 dogs; they were all stray dogs and in poor general condition. For this reason they were first kept several days at rest to improve their state of nutrition.

The diet before and after intervention was an ordinary uniform mixed diet.

TABLE 1.—*Effects of the Denervation of the Stem of the Liver*

Experiment No.	Animal No.	Date	Before Administration of Dextrose	Grams of Dextrose in 1,000 Cc. of Blood After Administration of 1.75 Gm. of Dextrose per Kilogram of Body Weight			
				½ Hr.	1 Hr.	2 Hr.	3 Hr.
1	1	5/18/32	0.89	1.34	1.19	1.07	0.80
2	1	5/21/32	1.01	1.35	1.23	1.00	0.76
		6/20/32	Denervation of the stem of the liver				
3	1	7/ 5/32	0.86	1.14	1.05	0.79	0.83
4	1	7/21/32	0.90	1.11	1.07	0.88	0.76
5	1	8/ 5/32	0.73	1.19	1.02	0.75	0.81
6	1	8/20/32	0.83	0.86	0.79	0.76	0.81
7	1	9/30/32	0.89	1.25	1.14	1.01	0.87
9	2	5/24/32	1.05	1.32	1.19	0.86	0.83
10	2	5/26/32	0.94	1.38	1.13	0.93	0.88
		6/20/32	Denervation of the stem of the liver				
11	2	7/ 6/32	0.96	1.22	1.09	0.99	0.89
12	2	7/20/32	0.79	1.16	1.07	0.86	0.82
13	2	8/ 6/32	0.80	1.05	1.02	0.91	0.83
14	2	8/21/32	0.90	1.20	1.17	0.83	0.81
15	2	9/21/32	0.98	1.38	1.13	0.75	0.80
16	3	5/19/32	0.86	1.27	1.10	1.08	0.70
17	3	5/29/32	0.91	1.25	1.14	0.95	0.83
		6/14/32	Denervation of the stem of the liver				
18	3	6/30/32	0.83	1.17	1.08	0.85	0.88
19	3	7/15/32	0.86	1.08	1.08	1.06	0.90
20	3	8/15/32	0.76	0.98	0.90	0.87	0.84
21	3	9/29/32	0.94	1.18	1.13	0.91	0.88
22	3	10/20/32	0.95	1.42	1.29	1.03	0.92
23	4	5/23/32	1.07	1.43	1.26	1.11	1.02
24	4	5/31/32	0.96	1.53	1.29	1.07	0.86
		6/14/32	Denervation of the stem of the liver				
25	4	7/10/32	0.94	1.25	1.16	1.03	0.96
26	4	8/16/32	0.93	1.18	0.86	0.88	0.85
27	4	8/28/32	0.57	1.08	1.04	0.75	0.76
28	4	9/28/32	0.81	1.28	1.14	1.07	0.81
29	4	10/22/32	0.93	1.50	1.33	1.19	1.00

The blood sugar after twenty-four hours of fasting and the curves after introduction through a Rehfuss tube of 1.75 Gm. of dextrose, dissolved in 2.5 cc. of water per kilogram of body weight, were repeatedly examined. Samples of blood were taken from the saphenous vein before the administration of dextrose and one half, one, two and three hours after the administration. The dog was left loose so that the rise in the blood sugar from fetters (*Fesselungshyperglykämie*) would not interfere with the results. At the necropsy pieces were taken from several organs for histologic examination.

Experiment No.	Animal No.	Date	Grams of Dextrose in 1,000 Cc. of Blood						Glycosuria, %	Kg.
			Before Administration of Dextrose	After Administration of Dextrose						
				½ Hr.	1 Hr.	2 Hr.	3 Hr.			
29	5	5/20/32	0.90	1.23	1.11	0.94	0.84		....	13.5
		5/22/32	Partial pancreatectomy (25.3 Gm.)							
30	5	6/ 6/32	1.67	1.92	2.50	2.95	2.38		3.8	11.5
31	5	6/22/32	1.96	2.10	2.92	2.14	2.40		4.6	11
32	5	7/24/32	2.14	2.39	2.52	3.43	2.78		5	10.3
		7/25/32	Denervation of the stem of the liver							
33	5	8/10/32	1.78	2.09	2.38	2.39	2.05		5	9.5
34	5	8/26/32	2.06	2.61	2.67	2.63	1.92		4.4	9.7
35	5	9/24/32	2.31	2.62	3.07	2.78	2.57		5.7	9.3
		10/ 2/32	Extirpation of the transplanted part of the pancreas (4.6 Gm.)							
36	5	10/ 2/32	3.43	4.88	5.20	4.52	3.85		13	9.4
37	5	10/ 3/32	3.78							
38	5	10/ 4/32	3.27	....	....	....	....		8.7	9.1
39	6	5/17/32	0.92	1.29	1.17	0.85	0.77		....	12
40	6	5/28/32	0.89	1.31	1.01	0.74	0.78		....	12
		6/ 2/32	Partial pancreatectomy (18 Gm.)							
41	6	6/21/32	1.25	1.61	2.19	2.06	1.35		1.15	11.5
42	6	7/29/32	1.34	2.05	2.28	1.90	1.29		....	....
43	6	8/ 1/32	1.36	1.94	2.09	1.64	1.33		1.37	10.9
44	6	9/ 1/32	1.49	2.09	2.33	1.55	1.30		1.90	10.5
		9/ 6/32	Denervation of the stem of the liver							
45	6	9/21/32	1.10	1.69	1.69	1.47	1.21		1.07	10.7
46	6	10/ 6/32	1.24	1.48	1.73	1.31	1.16		2	9.8
47	6	10/21/32	0.92	1.06	1.12	1.05	1.05		0.97	10.2
48	6	11/ 6/32	1.10	1.28	1.48	1.38	1.25		2.6	10.3
49	6	12/ 6/32	1.21	1.55	1.40	1.22	1.24		1.7	9.9
		12/ 9/32	Extirpation of the transplanted part of the pancreas (9.4 Gm.)							
50	6	12/10/32	4.5	....	....	....	....		5.6	9.5
51	6	12/11/32	4.1	....	....	....	....		6	9.7
52	7	5/15/32	0.96	1.56	1.20	0.94	0.87		....	14.5
53	7	5/30/32	0.99	1.31	1.13	0.94	0.79		....	14.5
		6/ 2/32	Partial pancreatectomy (29 Gm.)							
54	7	6/23/32	1.10	1.57	1.61	1.49	1.15		0.56	14
55	7	7/ 3/32	1.12	1.47	1.69	1.38	1.16		1.21	13.7
56	7	7/18/32	1.24	1.90	1.66	1.30	1.34		2.3	13.5
57	7	8/ 1/32	1.49	2.05	1.98	1.61	1.62		2.91	12.8
58	7	9/ 7/32	1.50	1.51	2.09	1.78	1.46		1.77	13.2
59	7	10/ 4/32	1.38	1.66	1.78	1.54	1.20		1.33	13
		10/ 8/32	Denervation of the stem of the liver							
60	7	10/23/32	1.00	1.31	1.24	1.06	1.07		0.71	12.7
61	7	11/ 8/32	1.05	1.16	1.19	1.15	1.06		0.77	13.1
62	7	11/23/32	0.92	1.08	0.98	0.89	0.95		0.33	13
63	7	12/ 7/32	1.28	1.34	1.63	1.61	1.21		3	12.5
64	7	12/22/32	1.22	1.37	1.88	1.42	1.28		2.43	12.3
65	7	1/ 7/33	1.45	1.65	1.73	1.65	1.37		1.90	12.6
		1/ 7/33	Extirpation of the transplanted part of the pancreas (10 Gm.)							
66	7	1/ 8/33	2.77	3.55	3.89	4.00	2.90		9	12
67	7	1/ 9/33	4.10	5.55	5.79	4.37	3.69		16	11.6
68	7	1/12/33	3.78	....	....	....	....		11	11.1
69	8	5/25/32	1.01	1.58	1.15	1.03	0.91		....	9.5
70	8	5/27/32	1.06	1.42	1.05	1.07	0.88		....	9.5
		6/ 8/32	Partial pancreatectomy (11 Gm.)							
71	8	6/21/32	1.38	1.73	2.10	1.46	1.43		2.13	9
72	8	7/ 7/32	1.91	2.95	3.06	2.70	2.06		3.20	9.1
73	8	7/23/32	2.21	2.52	3.25	2.00	2.12		3.55	8.6
74	8	8/ 7/32	2.11	2.85	2.95	2.35	1.98		1.94	8.7
75	8	8/22/32	1.60	3.00	3.01	3.09	1.90		4	8.4
76	8	9/10/32	2.06	2.53	2.93	2.11	2.11		5.90	8.2
		10/11/32	Denervation of the stem of the liver							
77	8	10/23/32	1.24	1.19	1.12	1.21	1.24		3.1	8
78	8	10/10/32	1.17	1.48	1.22	1.15	1.13		2.25	8.3
79	8	10/25/32	1.34	1.38	1.28	1.17	1.20		2.10	8.5
80	8	11/10/32	1.43	1.57	2.18	1.77	1.49		3.22	8.3
81	8	12/10/32	1.57	2.09	3.05	2.02	1.78		4.00	8.7
82	8	1/10/33	1.40	1.66	2.06	1.33	1.35		2.60	8.6
		1/13/33	Extirpation of the transplanted part of the pancreas (14 Gm.)							
83	8	1/14/33	2.90	2.99	3.44	4.50	3.00		10	8.4
84	8	1/16/33	4.23	....	....	....	....		13	7.9

46571

Experiment No.	Animal No.	Date	Before Administration of Dextrose	After Administration of Dextrose				Glycosuria, %	Kg.
				½ Hr.	1 Hr.	2 Hr.	3 Hr.		
S5	9	5/31/32	1.02	1.60	1.19	0.92	0.85	....	19
S6	9	6/ 4/32	0.S6	1.55	1.07	1.01	0.91	....	19
		6/ 8/32	Partial pancreatectomy (34 Gm.)						
S7	9	6/23/32	1.4S	2.50	1.S3	1.62	1.51	....	....
SS	9	7/ 7/32	1.37	1.98	1.90	2.13	1.71	1.S7	1S
S9	9	7/24/32	1.7S	2.65	2.35	1.69	1.S4	3.10	17.S
90	9	S/12/32	1.96	2.91	2.S5	2.30	2.00	4.30	17
		9/ 8/32	Denervation of the stem of the liver						
91	9	9/28/32	1.35	1.57	1.34	1.40	1.S9	2.70	16.6
92	9	10/14/32	1.31	1.95	1.50	1.27	1.25	....	....
93	9	11/29/32	1.21	1.25	1.59	1.30	1.16	3.15	17
94	9	12/12/32	1.47	1.69	1.47	1.3S	1.34	3	17
95	9	1/12/33	2.05	2.63	2.2S	1.90	1.60	5.60	16.3
96	9	1/17/33	1.76	2.39	2.07	1.79	1.65	4.30	16
		1/17/33	Extirpation of the transplanted part of the pancreas (11.7 Gm.)						
97	9	1/1S/33	2.77	2.94	5.10	2.56	2.69	7	16
9S	9	1/19/33	3.13	3.57	4.40	3.33	3.21	9	15.7
99	9	1/20/33	3.57	....	....	....	....	13	
100	9	1/20/33	3.11	....	....	....	....	6.30	15.3

General anesthesia was induced by morphine and ether. An incision just below and parallel to the right costal arch was made. After the abdominal cavity was opened, the stem of the liver was sought. The surgeon's left index finger was introduced into the foramen of Winslow; the hepatoduodenal ligament was then lifted and well exposed.

All the nerve filaments which run in or are interwoven over the hepatic arteries (after detachment of the gastroduodenal from the hepatoduodenal artery, to prevent interference with the pancreatic nerves) and all nerve filaments interwoven over the bile ducts and the principal portal vein were then accurately isolated and severed high up toward the liver. Moreover, for greater surety Doppler's isophenol (6 per cent phenol to which isomers of tricresol are added to neutralize its caustic action) was applied locally for about 2 cm. with a brush.

As may be seen in table 1, the blood sugar was not much lowered by denervation of the stem of the liver. I should say rather that it varies within the normal limits, although for some time (about three months) there is a tendency to settle near the minimum normal figures. According to many authors the normal readings in dogs are between 1.06 and 0.73 per cent (Macleod, Morgulis, Oppler and Rona, Pi Suñer and Puche and Houssay and co-workers).

When the blood sugar curves after administration of dextrose were plotted, a smaller rise and in some cases a marked end fall of the curve was observed (the posthyperglycemic hypoglycemia described by Depisch, Hasenöhrl, Rubino and Varela). In dog 1 a paradoxic curve was obtained three months after intervention. These findings, which however after four months diminished, the sugar content of the blood returning to, or even becoming higher than, preoperative values (e. g., in animal 4), were explained as signs of better carbohydrate tolerance.

PARTIAL AND COMPLETE EXTIRPATION OF THE PANCREAS

In another series of experiments I performed partial extirpation of the pancreas (about four fifths), cutting away the part which is supplied by the pancreaticoduodenal artery and by the splenic branches. The part supplied by the mesenteric blood vessels, which is easily recognizable because it retains its pinkish color while the rest is cold and cyanotic, was transplanted under the skin according to Hédon's method. The skin was protected with collargol ointment and cleaned with a dilute solution of hydrochloric acid. After recovery from the intervention, the course of the mild experimental diabetes was determined, and the effects of the denervation of the stem of the liver were studied two months later. Finally the transplanted part of the pancreas was taken away, so that the reactions could be studied in the same dog deprived completely of the pancreas. The results may be seen in table 2.

From the results of the dextrose tolerance test (table 2) it is evident that the partial extirpation of the pancreas caused in all cases a more or less marked diabetes, as was shown by the change in the general condition, by the hyperglycemia and by the presence of sugar in the urine (Benedict's test).

After denervation of the stem of the liver the apex of the blood sugar curve was lowered more or less; this was especially evident in dog 6. In some cases the figures of the single readings on the plotted curve are placed on a slightly jagged line, as in the case of dog 5 one month after the intervention and dog 6 one and a half months after the intervention. The initial readings for the blood sugar after fasting about one month after the intervention are also generally lower, and the final readings sometimes show a tendency toward posthyperglycemic hypoglycemia. In the case of dog 5, in which the partial extirpation of the pancreas was followed by a severe form of diabetes, the denervation of the stem of the liver had no favorable effects. The behavior of the alimentary hyperglycemia shows that the advantages obtained in the other cases were temporary, with a tendency to disappear in about three months and return to preoperative conditions; the intervention, moreover, did not modify the rapidly fatal course that is usually observed after extirpation of the graft of the remaining pancreatic tissue.

BILATERAL SPLANCHNICOTOMY

In a third series of experiments I investigated the effects of splanchnicotomy on the blood sugar. With the animal under anesthesia induced with morphine and ether, a median laparotomy incision was made; the greater and lesser splanchnic nerves were brought into evidence by the technic I have described in a previous paper. The nerves were then passed over a large loop of silk; a piece about 1.5 cm. long

was cut away, and the cut ends were bent and fixed in opposite directions. This was done because of their tendency to regeneration which is so great that de Takáts,[2] for the same reason, sutured the upper cut end of the nerve to the tenth intercostal nerve. The results may be seen in table 3. The remarks made about the denervation of the liver may be here repeated; they agree with what I stated relative to the suppression of the epinephrine function.[44]   .

TABLE 3.—*Effects of Section of the Splanchnic Nerve*

Experiment No.	Animal No.	Date	Before Administration of Dextrose	After Administration of 1.75 Gm. of Dextrose per Kilogram of Body Weight			
				½ Hr.	1 Hr.	2 Hr.	3 Hr.
101	10	6/ 9/32	0.99	1.32	1.11	0.95	0.89
102	10	6/12/32	1.01	1.39	1.17	1.00	1.00
		6/19/32	Section of the splanchnic nerve				
103	10	7/ 1/32	0.81	1.23	1.13	1.01	0.86
104	10	7/19/32	0.75	1.15	1.11	0.91	0.93
105	10	8/ 3/32	0.67	1.19	1.10	1.00	0.91
106	10	8/19/32	0.87	1.23	1.09	1.07	0.99
107	10	9/19/32	1.05	1.26	1.07	1.05	0.88
108	10	10/15/32	1.00	1.33	1.19	0.87	0.87
110	11	6/11/32	0.95	1.51	1.13	0.97	0.97
111	11	6/13/32	1.00	1.47	1.19	1.00	1.02
		6/19/32	Section of the splanchnic nerve				
112	11	7/ 8/32	1.05	1.27	1.20	1.11	1.03
113	11	8/26/32	0.78	1.37	1.12	0.93	1.03
114	11	8/ 9/32	0.78	1.12	1.05	1.05	0.83
115	11	8/18/32	0.87	1.18	1.04	0.85	0.81
116	11	9/ 6/32	0.91	1.29	1.09	1.03	1.00
117	11	10/ 8/32	0.91	1.39	1.21	1.00	1.04
117	12	6/ 7/32	0.96	1.43	1.14	0.90	0.91
		6/25/32	Section of the splanchnic nerve				
118	12	7/11/32	0.80	1.23	1.07	0.94	0.80
119	12	7/27/32	0.87	1.23	1.05	0.98	0.86
120	12	8/11/32	0.64	1.15	1.11	1.00	0.79
121	12	8/29/32	0.80	1.10	1.09	1.03	0.65
122	12	9/11/32	0.79	1.29	1.17	1.03	0.87
123	12	10/11/32	1.00	1.38	1.22	1.00	1.03
123	13	6/15/32	0.96	1.45	1.21	0.88	0.57
124	13	6/18/32	Section of the splanchnic nerve				
125	13	7/ 9/32	0.81	1.21	1.10	0.96	0.88
126	13	7/28/32	0.78	1.20	1.05	0.95	0.86
127	13	8/13/32	0.83	1.22	1.08	0.93	0.91
128	13	8/30/32	0.60	1.17	1.09	1.00	0.88
129	13	9/13/32	0.85	1.26	1.14	0.93	0.95
130	13	10/13/32	0.87	1.39	1.20	0.98	0.83

The fasting blood sugar falls inconstantly below the minimum normal readings, but the hypoglycemia is not marked. The blood sugar curves after administration of dextrose in general remain lower than before intervention for about two months afterward but later show a marked tendency to return to normal values. In some cases there are but slight variations, so that the plotted curve is a straight or slightly wavy line.

44. Ljvraga, P.: Surrenali e diabete: Contributo alla fisiopatologia dei surreni, Riv. di pat. sper. **10**:107, 1933.

Administration of the dextrose tolerance test according to the method described facilitates the observation of results not only in cases of mild or chronic diabetes of the Sandmeyer type but in cases of the severe condition that takes place after extirpation of the rest of the organ. This test showed that the beneficial results in animals submitted to splanchnicotomy were not more marked than those in animals deprived of the medullary adrenal tissue or with denervated livers (table 4). This statement results from a comparison of tables 2 and 4 of this paper with those of a previous paper.[44]

In the postmortem examination of my experimental animals, a considerable degree of congestion of the liver was observed; the organ was enlarged and of rather soft consistency and dark red in color in 2 dogs killed two weeks after denervation of the stem of the liver. These observations were more marked in 2 other animals killed two weeks after splanchnicotomy. Histologic sections showed a thinning of the radial cellular columns among the enlarged capillaries full of blood around the central vein of the lobule, which was widely distended (figs. 1 and 2). The cells were smaller than is normal, and the kernels were more deeply colored by hematoxylin than usual. The protoplasm was dark, often with several round vacuoles, which were shown by specific staining methods to contain fat.

In slices stained by the Vastarini-Cresi method glycogen was observed in the central part of the lobules in the form of a few small grains; in determinations by Pflüger's method the glycogen content was shown to be less than 1 per cent. In dogs 5 and 14 to 18, necropsy was performed about three months after the denervation of the liver and the splanchnicotomy respectively. The observations described were less marked; there were, however, vascular congestion of the central and perilobular blood vessels and a fair quantity of fat in the cells of the liver with a relative scarceness of glycogen as revealed by the Vastarini-Cresi stain. Histologic sections of the stem of the liver, when stained by Cajal's method, showed a greater quantity of connective tissue and rare slender nerve fibers, generally attached to the portal vein. At necropsy on the dogs studied in tables 2 and 4, the liver was seen to be normal in size; fat was abundant and diffusely distributed in the hepatic cells, as shown by the scarlet red stain, and rare, small blocks of glycogen were present, especially in the central part of the lobule, as seen by the Vastarini-Cresi method, the quantity being 3.3 to 4.5 per cent as analyzed by Pflüger's method.

The adrenals of animals in which the stem of the liver was denervated showed only hyperemia, especially in the medullary part, two weeks after intervention; the structure was seen to be normal if examined in later periods. In dogs submitted to bilateral splanchnicotomy,

Experiment No.	Animal No.	Date	Before Administration of Dextrose	After Administration of Dextrose ½ Hr.	1 Hr.	2 Hr.	3 Hr.	Glycosuria, %	Kg.
131	14	1/18/33	1.00	1.49	0.93	1.05	0.86	....	20
132	14	1/21/33	1.03	1.42	1.07	1.00	0.84	....	20
	14	1/28/33	Partial pancreatectomy (26 Gm.)						
133	14	2/12/33	1.50	1.73	1.55	1.37	1.44	2.30	18.9
134	14	2/22/33	1.62	2.19	2.31	2.05	1.90	....	....
135	14	3/23/33	2.11	2.60	2.01	2.00	2.10	3	19
	14	3/24/33	Section of the splanchnic nerve						
136	14	4/ 8/33	1.38	1.67	1.45	1.33	1.40	2.05	18.5
137	14	4/24/33	1.31	1.53	1.60	1.29	1.25	....	....
138	14	5/ 8/33	1.27	1.39	1.48	1.36	1.30	2.40	18.8
139	14	5/25/33	1.32	1.70	1.73	1.42	1.40	2	19
140	14	6/ 8/33	1.54	1.81	1.41	1.41	1.38	....	....
145	14	7/ 8/33	1.37	1.76	1.87	1.39	1.42	3.35	19.4
	14	7/ 9/33	Extirpation of the transplanted part of the pancreas (11 Gm.)						
146	14	7/ 9/33	2.53	3.23	3.70	2.42	2.60	7.45	19
147	14	7/11/33	3.70	4.51	5.10	5.00	4.20	12.50	18.7
147	15	1/19/33	0.95	1.38	1.07	0.93	0.93	....	13
148	15	1/22/33	0.98	1.39	0.99	0.90	0.91	....	13
	15	1/25/33	Partial pancreatectomy (19.7 Gm.)						
149	15	2/ 5/33	2.00	2.39	3.10	2.64	2.06	3.10	12.4
150	15	2/20/33	1.60	2.55	2.97	1.93	1.75	....	....
151	15	3/ 7/33	2.09	3.00	3.34	2.80	1.94	4.20	12
152	15	3/13/33	Section of the splanchnic nerve						
152	15	3/31/33	2.00	3.01	3.09	2.34	1.92	3.50	11.8
153	15	4/11/33	1.55	2.35	2.60	1.90	1.60	3.70	11.8
154	15	4/26/33	1.62	2.70	2.44	1.74	1.78	....	....
155	15	5/13/33	1.49	1.53	2.00	2.07	1.60	4	11.6
156	15	6/13/33	1.58	2.10	2.85	1.66	1.62	4.18	11.3
157	15	7/13/33	1.38	1.86	2.15	1.96	1.73	4.37	11.5
159	15	7/17/33	Extirpation of the transplanted part of the pancreas (9.5 Gm.)						
158	15	7/19/33	2.28						
159	15	7/21/33	3.34	4.00	4.70	4.18	3.57	15	11
160	15	7/21/33	4.55						
161	16	1/26/33	1.01	1.65	1.10	0.96	0.87	....	15
162	16	1/31/33	0.96	1.59	1.00	1.00	0.90	....	15
	16	2/ 3/33	Partial pancreatectomy (20 Gm.)						
163	16	2/19/33	2.31	2.87	2.70	2.55	2.55	4.70	14.6
164	16	3/ 6/33	2.04	3.56	3.11	3.00	3.15	5.10	14.1
165	16	4/19/33	3.59	3.70	4.46	3.98	3.06	8.40	13.8
	16	4/20/33	Section of the splanchnic nerve						
166	16	5/ 7/33	2.77	2.88	2.89	2.64	2.70		
167	16	5/22/33	2.58	3.00	3.21	2.97	2.60	6	14
168	16	6/10/33	2.88	2.97	3.49	3.15	3.21	6.10	13.5
169	16	6/25/33	2.15	2.51	2.86	2.48	2.20	4.90	13.1
170	16	7/26/33	1.90	2.21	2.55	2.30	1.89	5.13	13
171	16	8/22/33	2.28	3.00	3.74	2.11	2.18	4.87	12.8
172	16	8/26/33	Extirpation of the transplanted part of the pancreas (7.5 Gm.)						
173	16	8/26/33	4.23						
174	16	8/28/33	5.18	....	....	....	....	16	12.3
175	16	8/30/33	3.87	....	....	....	....	11	12.1
176	17	2/ 1/33	0.95	1.28	0.88	0.95	0.89	....	11
177	17	2/ 8/33	0.97	1.34	0.87	0.81	0.92	....	11
	17	2/13/33	Partial pancreatectomy (12 Gm.)						
178	17	2/28/33	1.95	3.11	3.25	1.85	2.01	4	10.4
179	17	3/16/33	2.21	3.06	3.59	2.00	2.19	2.88	10.5
180	17	4/16/33	2.10	2.52	2.91	2.70	2.00		
	17	4/18/33	Section of the splanchnic nerve						
181	17	5/ 3/33	1.83	2.35	2.85	1.90	1.85		
182	17	5/19/33	1.91	2.77	2.74	2.35	1.90	3.70	10.3
183	17	6/ 5/33	1.60	2.44	2.50	2.28	1.72		
184	17	6/21/33	1.58	1.97	1.99	2.00	1.63	3.65	10.5
185	17	7/22/33	1.49	2.00	1.88	1.94	1.56	3	10.5
186	17	8/25/33	1.77	2.47	2.89	1.89	1.64		
	17	8/27/33	Extirpation of the transplanted part of the pancreas (4.7 Gm.)						
187	17	8/27/33	3.13	3.78	3.65	2.67	2.98	9.70	10
188	17	8/29/33	4.58	....	....	....	....	12	9.7
189	17	8/30/33	4.10	....	....	....	....	8.90	9.5
190	18	2/10/33	1.02	1.45	0.90	0.87	0.90	....	11.9
191	18	2/15/33	1.05	1.47	1.01	0.99	0.89	....	11.8
	18	2/18/33	Partial pancreatectomy (8 Gm.)						
192	18	3/ 8/33	1.33	1.67	1.46	1.29	1.36	0.99	11.4
193	18	3/22/33	1.49	1.68	1.71	1.54	1.50		
194	18	4/ 6/33	1.78	2.05	2.15	2.00	1.69	1.25	11.4
195	18	4/27/33	1.66	2.28	2.54	2.00	1.77	1.50	11.5
	18	4/30/33	Section of the splanchnic nerve						
196	18	5/15/33	1.38	1.70	1.91	1.49	1.41	1	11.1
197	18	5/30/33	1.22	1.24	1.17	1.16	1.20	0.78	
198	18	6/16/33	1.30	1.51	1.57	1.29	1.19		
199	18	6/30/33	1.17	1.23	1.35	1.15	1.15	1.10	10.9
200	18	7/25/33	1.41	1.63	1.71	1.30	1.34		
201	18	8/24/33	1.50	1.74	1.88	1.44	1.36	1.70	11.2
	18	8/28/33	Extirpation of the transplanted part of the pancreas						
202	18	8/28/33	2.45	3.48	3.56	3.09	2.29	5.60	11
203	18	8/30/33	3.70	4.76	5.43	4.23	4.10	. 9.78	10.7
204	18	9/ 2/33	4.67						
205	18	9/ 2/33	4.00						

on the contrary, the adrenals were much more congested two weeks after intervention (fig. 3), and the vascular congestion was clearly visible also in the cortical tissue. In dogs killed in later periods the

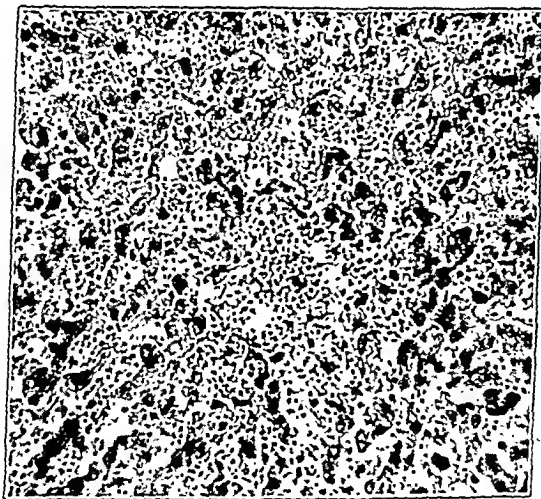Fig. 1.—Liver two weeks after denervation of the hilus.

Fig. 2.—Liver two weeks after bilateral section of the splanchnic nerve.

connective tissue was markedly increased, especially in the medullary part, where the cells were small with faintly staining kernels; the chromaffin test with Wiesel's method gave a weakly positive or even a negative reaction. Other organs were normal.

Summarizing the foregoing biochemical and histologic data, I may say that in general I have observed the same results as in animals deprived of the medullary adrenal tissue. In short, the same changes of the fasting blood sugar toward the minimum normal values were observed. Sometimes there were slight, flighty drops below normal,. but these were never marked or accompanied by noticeable outward signs. The blood sugar curves in the dextrose tolerance test also were somewhat lower in general than before intervention; in some cases no change took place (experiments 47 and 62). These essential facts observed agree substantially with the statements of other authors. On the basis of such data a better carbohydrate tolerance has been claimed. On these findings were founded the hopes of surgical therapy for diabetes.
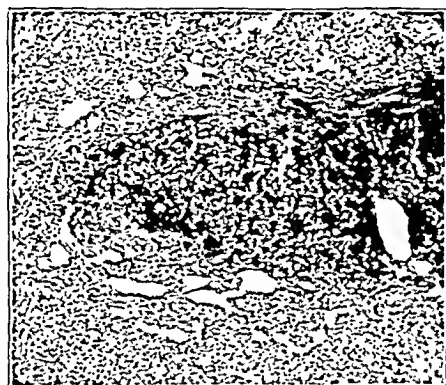

Fig. 3.—Adrenal gland two weeks after bilateral section of the splanchnic nerve.

The similarity of the findings after various interventions (denervation of the liver or suppression of the adrenal function by denervation of the adrenals, medullectomy or splanchnicotomy) proves again the existence of a hepatic-adrenal-sympathetic chain, whose blocking, in any district or in one of the stations along it, has no practical influence, in its final effects, on the sugar content of the blood. On the basis of such phenomena, can a better sugar tolerance be claimed? May a favorable influence on the experimental diabetic condition be alleged? I doubt it very much.

The fasting blood sugar, as has been stated, presents in dogs after denervation of the liver, and more markedly after bilateral splanchnicotomy, variations toward the lower limits of normal values, which, however, cannot lead to any definite conclusions. The figures considered by most authors as representing the normal sugar content of the blood in dogs range from 0.73 to 1.06 per cent; but these authors have not mentioned Negrin's opinion, not shared by all of them, that the sugar

content of the blood in dogs and cats is unstable, or Bang's opinion, which is hardly acceptable, denying even the possibility of defining the average in these animals. I believe that the findings of the dextrose tolerance test, as well as the readings for the fasting blood sugar, can be explained as will be stated.

Since Albertoni's excellent research, it is well known that the liver regulates the distribution and consumption of the dextrose that arrives through the portal circulation, functioning, according to the galenic simile, as a great storehouse in a well governed city. Albertoni in his experimental search for the seat of the changes in carbohydrate in the body, observed that in rabbits after twenty-four hours of fasting relatively large quantities of dextrose (20 Gm.) are withheld by the liver, not interfering, therefore, with the sugar content of the blood. This observation of the Italian physiologist is confirmed by many clinical and experimental observations published in medical literature.

The blood sugar curves in the dextrose tolerance test are probably influenced, moreover, by the condition of the barrier which the liver interposes between the intestines, which are the source, and the general circulation, which is the route of distribution, of the carbohydrates. In fact, Löffler, Grunke and Hess, Pollak, Wachsmuth and Löweneck and previously Hetény (1926) explained the smaller rise in the blood sugar or its failure to change if the introduction of carbohydrates is preceded by injection of ergotamine (more marked if atropine is associated) by the slowing of the portal-hepatic circulation and the consequent smaller deposition of glycogen, which is in turn associated with a correspondingly evident increase of fat. The scarceness of glycogen in the liver and the consequently more active fixation of the dextrose arriving from the portal circulation would explain, according to the conclusions of Albertoni, confirmed by others, the curves with a lower apex and the nearly level curves.

The mechanism of the hyperglycemia that occurs after administration of sugar has been the subject of much debate in past years. Some authors (Zunz and La Barre) have described the involvement of central and peripheral actions due to the dextrose itself, and others (Staub, Traugott, Pollak, Eisnar and Forster, Depisch and Hasenhörl) have mentioned the probability of a reflex action of the mucosa of the duodenum on the liver. On the other hand, the so-called reabsorption theory (Pollak, Gigon, Cori, Staub and La Barre), as well as the theory of stimulus (Rubino and Varela, Umberg, Rosemberg, Hetény and Pogany), is certainly as susceptible to criticism as that which I have adopted. My theory, moreover, is more generally accepted and is supported by experimental and clinical evidence.

I have already mentioned the intense stasis which takes place in the liver after denervation of its stem; this was described also by

de Fermo [38] and closely resembles that which takes place after denervation of the adrenals or removal of the adrenal medullary tissue (Ljvraga [44]). Such hyperemia reaches its maximum after bilateral splanchnicotomy, extending to nearly all the areas which are supplied by these nerves, as has been reported by Pende and Pellegrino. Moreover, I showed the consequent lessening of the glycogen by histologic methods, confirmed by measurements made by Pflüger's method; this phenomenon was produced under the same conditions also by Pico Estrada and by Houssay and his school.

These two positively ascertained facts are in themselves capable of explaining the blood sugar readings after fasting and in the dextrose tolerance test. On this point I must recall my interpretation of the so-called *Karenzhypoglykämie* (Mansfeld's phenomenon) after massive ligature of the pancreas. A fall in the sugar content of the blood was observed twenty-four hours after such intervention and became more marked after two or three days of fasting. [5]

Some authors have reported, besides a better carbohydrate tolerance in general, a lower hyperglycemia after administration of epinephrine and a greater sensibility to insulin. Since epinephrine causes a discharge of glycogen from the liver, mobilizing the dextrose stored there in condensed form, it is evident that the smaller deposit or almost complete lack of glycogen is the cause of the lower hyperglycemia after administration of epinephrine; it is therefore unnecessary to state that the reaction is hindered by an increase of insulin in the blood.

I maintain this opinion also because in nature the simplest explanations are always those which are most probably true (Murri). The foregoing conclusion, moreover, accounts for the higher sensibility to insulin, because the liver's aid in the return to normal of the blood sugar is unstable.

CONCLUSIONS

The ligature of ducts and the massive ligature of the pancreas have proved failures as possible surgical cures for diabetes.

The conclusions of a previous paper of mine [5] have been openly confirmed by de Takáts and his co-workers [45] and Hüttl, [1] who tried the operation on man, and by Linhardt's significant silence.

In the modified pancreas, atrophic tissue, which has lost its external secretive function in the involution caused by inactivity, has been mistaken for functionally active insular tissue, which, indeed, it resembles morphologically. This fact explains why some authors have been led to describe, histopatholgically, insular hyperplasia and regeneration, which however did not correspond to an increase in the secretion of insulin proved by permanent improvement or real clinical recovery. I have

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45. Footnotes 2, 29, 30 and 33.

proved instead in the paper to which I have referred that the production of insulin is low after such intervention. This fact is established by the low urinary elimination (demonstrated by Collip's method), by the behavior of the blood sugar when tested by administration of dextrose and by the hepatic glycogen, determinations of which were made in freshly killed dogs by Pflüger's method.

The ligature of the ducts of the salivary glands in general, and especially of the parotid gland, has given results which do not encourage this practice. Two reasons for this failure are the lack of evidence of an increased internal secretion capable of lowering the abnormally high sugar content of the blood, which view I have already set forth (1932),[46] and the inability of the intervention to increase, as some authors believe, the insulin-producing activity of a pancreas having an altered insular tissue and therefore incapable of responding. This procedure, which because of its easy execution could be performed even on ambulatory patients (Gohrbandt), has now lost all credit.

The methods whose purpose is to weaken the anti-insulinic system of organs in order to restore the balance lost by the weakening of the blood sugar reducing mechanisms, especially the pancreas, have not justified the hopeful trust placed in them. Perhaps the choice of the cases in which such intervention is advisable is rather difficult. De Takáts[2] suggested two tests, resistance to insulin and certainty of reaction to ergotamine. Ciceri and Gabrielli[32] suggested previous splanchnic anesthesia as a test.

According to Pollak's investigations, the problem is unfortunately not so simple. He observed that in patients whose blood sugar was favorably influenced by ergotamine the drug would suddenly and without any appreciable reason become apparently inactive. Pollak stated moreover that, although the sugar content of the blood was nearer to normal, he had not been able to observe improvement in the general conditions or an increase in weight after treatment by insulin. This statement is confirmed by an observation of Giordano in 1 of his patients submitted to bilateral denervation of the adrenals. In this case the sugar content of the blood diminished, as did the urinary excretion of sugar, but nevertheless the diabetic gangrene existing was uninfluenced.

In my previous publications it was stated that the predominance of this antagonistic system is not to be considered as absolute, but in relation to the opposing neurohormonic constellation (Pende).

Therefore, referring to intervention on the adrenals, I then expressed my apprehension that, since persons suffering from diabetes maintain

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46. Ljvraga, P.: Studio sperimentale sulla legatura dei dotti escretori e sulla enervazione delle ghiandole salivari con speciale riguardo alla glicemia. Riv. di pat. sper. 8:68, 1932.

their physiologic volume of epinephine, the intervention might provoke an adrenal insufficiency in subjects already suffering from an insular insufficiency. This view was confirmed by a communication from Wilder, Foster and Pemberton,[16] who observed an improvement of the diabetic condition after total thyroidectomy, which, however, was associated with the appearance of the first signs of myxedema; in this condition I have previously described hypertrophy and hyperplasia of Langerhans' islands.[47] Thyroid extracts improved the condition but caused a return of the diabetes.

Rogoff [21] referred (1936) to a case of Addison's disease in a man aged 25, following bilateral denervation, in two stages, of the adrenal glands as an antidiabetic measure. About seven months after the second intervention, the first signs of a subacute hypoadrenalism appeared, which resulted in the patient's death in the course of a year. On the basis of this case Rogoff was drawn to share fully with me the opinion I have expressed: "This case illustrates the serious danger of attempting adrenal surgery for the correction of various ailments supposedly related with disturbed adrenal function."

The denervation of the stem of the liver in turn has proved to deserve no better consideration as a surgical cure for diabetes. The lowering of the sugar content of the blood both during fasting and after administration of dextrose in dogs with mild experimental diabetes from partial pancreatectomy does not suggest, when compared with that in normal dogs, any evident improvement of the diabetic condition. This observation, which applies also to those interventions which attack the adrenals, either in their tissue or in their function, is confirmed by other observations of the negative influence these operations exert on the severe experimental diabetes provoked by pancreatectomy. Komatsu,[39] Depisch, Hasenhörl and Schönbauer [34] and other authors have expressed agreement with this view. In fact, the short successive course of the disease was the same as is usually observed after pancreatectomy, as stated in my previous papers.

The observations of Elias and Waller [48] make still more difficult the far from simple interpretation of the conditions observed after extirpation of portions of the pancreas. These authors observed in dogs a spontaneous improvement of the renal excretion of sugar after a short time, while the carbohydrate tolerance increased and even surpassed the normal level. Successive partial extirpations had the same effect as long as the remaining part was not too small. Similar research by Komatsu [39] gave like results.

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47. Ljvraga, P.: Effetti della tiroidectomia sulle isole di Langerhans, Ztschr. f. Zellforsch. u. mikr. Anat. **22**:232, 1935.
48. Elias, H., and Waller, in discussion on Depisch, Hasenöhrl and Schönbauer.[34b]

It can then be concluded that in procedures affecting the hepatic-adrenal-sympathetic chain, as in those affecting the pituitary or the thyroid gland, some influence is certainly exerted on factors involved in the metabolism of carbohydrate, but only in an unstable manner and after occasional stimulation. They are all, in general, so to speak, accessory safety regulators of the blood sugar; moreover, sometimes the changes in the sugar content of the blood may even be due to secondary interferences, as often happens in natural phenomena with a large field of action.

To mention again the denervation of the stem of the liver, I must finally recall that the effects of this intervention are also partly annulled, at least in the extrainsular forms of diabetes, by the facts brought out by Macleod and Pearce,[35] Pollak, Freund and Schagentweit, Ljvraga and others. These authors proved, in fact, that epinephrine retains its hyperglycemia-producing power even after denervation of the liver; Elliot[49] therefore concluded that epinephrine acts, not on the nerves, but more peripherally, on what he calls the myoneural junction, which Langley has called the receptive substance.

References not cited in this article are to be found in my previous papers (footnotes 5, 6, 44, 46 and 47).

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49. Elliott, T. R.: The Control of the Suprarenal Glands by the Splanchnic Nerves, J. Physiol. **44:**374, 1912.

BENIGN TUMORS OF THE BREAST

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Fibroepithelial tumor (fibroadenoma) occurring in the female is of special interest, not only because it is entirely benign but also because, as it occurs frequently in young persons, the physician is often called on for reassurance.

In the six year period from 1931 to 1936 inclusive, 2,585 patients consulted the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital (formerly Stuyvesant Square Hospital) for disorders localized in the breast (table 1).

TABLE 1.—*Diseases of the Breast*

Condition	Cases	Percentage
Definitely benign tumor..........	722	28.0
Probably benign*............	59	2.3
Malignant tumor†...................	469	18.0
Probably malignant tumor*...........	41	1.5
Functional disturbance.................	1,028	40.0
Inflammatory conditions.........	215	8.2
No pathologic condition.....................	51	2.0

* Clinical diagnosis without pathologic examination.
† Including 449 carcinomas, 18 instances of Paget's disease, 2 sarcomas, 1 melanoma.

The benign tumors included adenoma, cystadenoma, fibroadenoma, fibroma, galactocele, hemangioma, lipoma, lymphangioma, neurofibroma and papilloma.

It is of interest that benign tumors outnumbered malignant tumors. Some years ago statistics showed a reverse order, for at the Halstead Clinic 80 per cent of tumors were malignant, while Erdmann [1] found 56 per cent to be malignant. In the present series only 39 per cent were malignant. This decrease probably indicates a more intelligent attitude of the public, reflected in an earlier consultation of the physician than was customary a few years ago.

The present paper will deal only with benign fibroepithelial tumors which have been removed surgically and of which the diagnosis has been confirmed by pathologic examination.

1. Erdmann, J. F.: Tumors of the Breast, South. Surgeon 3:277 (Dec.) 1934.

The records show that there were 174 cases of surgically treated fibroadenoma of the female breast. There were also 39 cases of fibroadenoma of the male breast so treated, but this series has been presented elsewhere.[2]

CLINICAL PICTURE

Constitutional Type and Age Incidence.—There may be inherited predisposition to mammary tumor, possibly on an endocrine basis. Burkhardt observed fibroadenoma in the left breast of each of twin girls. The tumor was of the same character in each of the two. This would seem to point to the possibility of familial influence.

The patients in my series were well developed and, in the main, well nourished. The slender, boyish type [3] of figure was infrequent. Some of the patients were of a nervous constitution, but in general there were no outward signs which might be said to be characteristic of the presence of a growth.

The age range is shown in table 2.

From these figures it is seen that the earliest age at which the "lump" was first noticed was 11 years and the latest 64. Sellers

TABLE 2.—*Age Incidence of Fibroadenoma*

Age	10-15	15-20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65
Number of cases	4	44	47	33	18	16	7	2	1	2	1

reported the occurrence of a large fibroadenoma in a girl aged 12; this is exceptional. If the age incidence of fibroadenoma of the female breast is expressed by a graph, it is clear that there is a steep rise, which reaches a peak at the age of 23 and abruptly descends after the thirtieth year. These figures are based on information given by the patients, which is necessarily inaccurate, since a relatively longer period must have elapsed before the tumor attracted notice. Taking into consideration the slow growth of most such tumors, one may assume that the growth probably arises at puberty or shortly after. Coinciding with the onset of menstruation at an average age of 13, such tumor formation would seem to correspond to the active sexual life of the female. If this graph is compared with that obtained from the study of benign fibrous tumors of the male breast it is seen that in the female breast this type of tumor develops most frequently under the age of 30, while in the male a second peak of incidence is found between the fiftieth and the eightieth year. One may say, then, that benign tumors of the breast seem to develop in the male during adolescence and senility, that is,

2. de Cholnoky, T.: Benign Fibrous Tumors of the Male Breast, Am. J. Surg. **30**:298 (Nov.) 1935.

3. Taylor, H. C., Jr.: Evidence for Endocrine Factor in the Etiology of Mammary Tumors, Am. J. Cancer **27**:525 (July) 1936.

during periods of life in which endocrine disturbances are most likely to occur, whereas in the female such formation seems to take place at about the second decade of life, that is, when endocrine activity is most intense.

In this series all patients were white except 1, a Negress aged 25 in whom fibroadenoma developed in both breasts within a period of five years.

Marital Status.—In this series 71 patients were single, 91 married, 3 divorced and 3 widowed. The marital status of 6 was unknown.
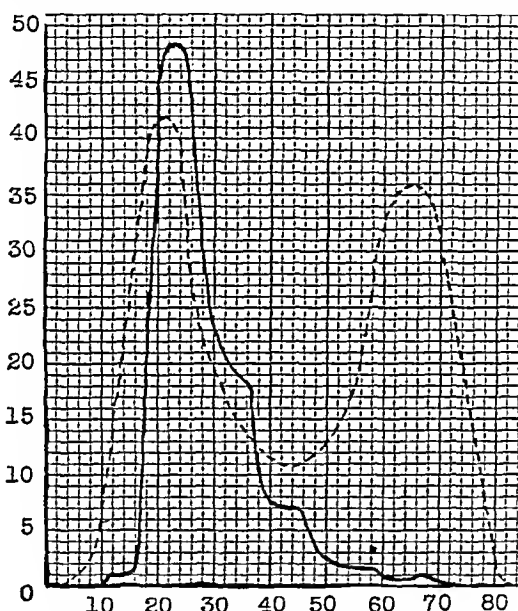
Incidence of fibroadenoma of the breast. The continuous line shows the distribution of fibroadenoma of the female breast. The interrupted line illustrates the occurrence of fibroadenomas of the male breast, multiplied by 6 (ratio 1 : 6). The vertical numbers indicate the number of cases; the horizontal numbers, the age incidence.

Occupation.—The patients were classified as to occupation as follows: housewives, 86; office workers, 48; saleswomen, 12; factory workers, 8; telephone operators, 4; and miscellaneous, 16.

Family History.—It is of interest that 23 (13.2 per cent) reported the occurrence of malignant tumors among blood relations, but this percentage is only slightly higher than that commonly accepted for cancer, 10 per cent, and is probably of no significance. A history of "tumor" in the family was given by 4 other patients. These histories may be analyzed as follows: For 7 patients there was a history of

carcinoma of the stomach, the lip, the larynx or the mouth of the father; 9 stated that the mother had died of carcinoma of the stomach or of the nose; 3 described the occurrence of carcinoma in the grandmother, and 1, in an uncle; 3 patients had sisters who had been operated on for "breast tumors."

TABLE 3.—*Number and Percentage of Excised Tumors* *

	Number Among Benign Tumors				Total	
	Female	Percentage	Male	Percentage	Number	Percentage
1. Malformations						
Accessory breast..............	36	5.2	..	....	36	1.4
Accessory nipple..............	7	0.8	..	....	7	0.2
2. Fibroepithelial tumors						
Adenoma..................	40	5.5	..	....	40	1.6
Fibroadenoma................	174	29.5	39	5.4	213	8.2
Papilloma						
Nipple.....................	3	0.3	0	....	55	2.1
Skin......................	23	1.0	3	0.2	26	1.0
Duct......................	26	1.2	0	....	26	1.0
3. Cystic tumors						
Cystadenoma.................	220	30.4	..	....	220	8.6
Galactocele..................	2	0.02	..	....	2	0.07
Sebaceous cysts..............	60	7.6	11	1.5	71	2.4
4. Connective tissue tumors						
Fibroma.....................	20	2.8	4	0.2	24	1.0
Lipoma.....................	26	3.7	1	4.0	27	1.0
Hemangioma.................	9	1.0	..	...	9	0.3
Lymphangioma..............	2	0.2	..	...	2	0.07
Neurofibroma...............	3	0.3	..	...	3	0.1

* Diagnosis confirmed by pathologic report.

TABLE 4.—*Comparative Incidence of Benign and Malignant Tumors*

All tumors (50% of all cases of mammary disease).....................................	1,291
Benign...	781 (61%)
Malignant..	510 (39%)
Fibroadenoma	
Total patients (20.9% of all tumors and 34.5% of benign tumors)...............	270
Operated on...	174 (64%)
Female patients...	229 (85%)
Male patients..	41 (15%)
Male patients operated on...	39 (95%)

The ratio of 270 fibroadenomas to malignant tumors (510) approximates 1:2

Personal History.—The average age at onset of menstruation was 13 to 14. For only 8 per cent of the patients was the age of onset 16 or 17. In the majority of cases the periods were regular. In 8 per cent they were irregular, and dysmenorrhea was noted in 10 per cent. Pregnancy has been experienced by 48 patients (27.5 per cent), and these had had from one to five children. Five, or 3 per cent, had a history of miscarriage. These facts would seem to bear out Taylor's statement that fibroadenoma is found most frequently in nulliparas (63 per cent) with relatively undeveloped pelvic organs. The develop-

ment of the growths, according to my observations, does not seem to be influenced by marital status or by pregnancy.

The length of time elapsing between observation of the "lump" by the patient and the seeking of medical advice ranged from one week to twelve years. The following table gives the time distribution:

TABLE 5.—*Duration of Lesion Before Examination*

Cases	Time from First Noting of "Lump" to Seeking of Advice
10	1 week
16	Within 1 month
29	Within 3 months
24	Within 6 months
10	Within 1 year
32	Within 2 years
11	Within 3 years
6	4 years
4	5 years
9	6 years
3	10 years
5	12 years
15	Not known

In only 1 case was the growth discovered in the course of routine physical examination. The patient had come to the clinic for advice relating to another ailment.

Personal Surgical History: Abscesses occurring in the same breast in which the tumor was localized were mentioned in the history of 2 of my patients. A previous hysterectomy had been performed on 1 patient at the age of 28. A year previously she had been operated on for fibroadenoma of the breast, of five years' duration. One patient had undergone thyroidectomy. Two had thyroid goiter seven years after the surgical removal of a mammary tumor (?), and 1 had cancer two years after operation. Radical mastectomy was performed on 2 patients, aged 45 and 43 respectively, in whose cases mistaken clinical diagnosis of carcinoma had been made.

Localization.—In 88 patients the tumor was localized in the right breast, and in 86, in the left.

The growth was situated at the upper outer quadrant of the right breast in 44 instances, at the lower outer quadrant in 10, at the upper inner quadrant in 8, and at the lower inner quadrant in 5; it was situated in the upper middle toward the head in 3, to the left of the mid-portion in 3, to the right of the midportion in 5 and caudad at the midregion in 5; it was located centrally in the breast in 2, and the location was not stated on the chart in 3. It is interesting to note from these figures that 50 per cent of tumors of the right breast occur in the upper outer quadrant. This percentage is raised to 61 if one includes the tumors in the borderline of this section.

The distribution of tumors of the left breast was similar except that there was a slight preponderance of growths localized in the outer quadrants.

The study of age in relation to location showed nothing significant.

Multiplicity and Recurrence.—The tumors were single in the great majority of cases. Geschickter[4] reported an incidence of bilateral involvement of 17 per cent, and Smith and Mark, of 3 per cent. Oliver and Major[5] reported a percentage of 15.75 per cent. In my series 6 patients (3.4 per cent) had tumors in both breasts simultaneously. Four had one tumor in each breast, and 2 had two in the right breast and one in the left; in all, the lesions had developed during a period of five years. In 2 cases the tumors were multiple (1.4 per cent) and appeared in the right breast within a few months.

Recurrence after complete removal of the tumor does not take place, but recurrence in the sense of new tumor formation in the same area, elsewhere in the breast or in the other gland is sometimes observed. An instance of this sort is the case reported by Payer, who removed nine fibroadenomas from both breasts of a young woman within four years. In my series recurrence took place in 6 patients (3.4 per cent); in 5 it was observed within two years, and from 1 five tumors were removed from the same gland within one year.

Size.—The size of the tumor usually varies with the duration, but in this series no definite relation between duration and size could be noted. The growth of the tumor is slow, although some patients exhibit a more rapid growth than others within the same period. Even considering the fact that a tumor may remain unnoticed for a long period, one must admit that some growths are "stationary." Several patients definitely stated that the lump had remained about the same size for years. Others observed rapid increase in its size within weeks or months.

Six patients were examined early, when the round or oval tumor was about 5 mm. in diameter. Eighteen when first seen had a lump 1 cm. in diameter. In 28 cases the size of the tumor was 1.5 cm.; in 36, 2 cm.; in 18, 2.5 cm.; in 10, 3 cm.; in 15, 4 cm.; in 9, 5 cm.; in 4, 6 cm.; in 4, 7 cm. Six patients had tumors 8, 9, 10, 12 and 15 cm. in diameter. In 20 cases no exact measurements were noted. The largest tumor measured 15 by 12 cm. It was removed from the breast

4. Geschickter, C. F.; Lewis, D., and Hartman, C. G.: Tumors of Breast Related to the Oestrin Hormone, Am. J. Cancer **21**:828 (Aug.) 1934.

5. Oliver, R. L., and Major, R. C.: Cyclomastopathy: Physiopathological Conception of Some Benign Breast Tumors, with Analysis of Four Hundred Cases, Am. J. Cancer **21**:1 (May) 1934.

of a patient aged 38, who had had the growth for five years. Approximately three fourths of my patients came for operation before the tumor had reached a diameter of 3 cm.

Fibroadenomas of enormous size have been reported. In Ashwell's case the tumor had a gross weight of 29 pounds (13.2 Kg.). Mackenzie [6] described one weighing 35 pounds (15.9 Kg.); the patient had been for years in the hands of religious revivalists and faith healers. Vos [7] made a comparative study of the fibroadenomas occurring in the white and in the native population of the colonies of the Netherlands and found that in the natives the growths attained a decidedly larger size before a surgeon was consulted.

ETIOLOGY

Trauma was mentioned in 3 per cent of my own cases, but the patients were unable to state the exact location of the injury, which was commonly designated as a "baby kick" or some similar mild trauma. One patient, 44 years of age, in whom the tumor was of four months' duration, attributed it to a kick by a horse suffered seven years before! It seems to me that trauma plays a minor role, if any, in the causation of the tumor, and that it serves rather the function of revealing a tumor already present.

While the causes underlying the formation of fibroadenoma are still being sought, clinical and some experimental evidence indicates that it is probably due to some hormonal influence. Since the presentation of Ribbert's theory of embryonal rests which have lost their correlation with the remainder of the mammary gland, Dietrich, Fragenheim, Moszkowski and others have concluded that chronic mammary disease is responsible for the development of fibroepithelial tumor.

Stimulus for further research was imparted by Rosenburg's [8] observation that the breast takes part in the sexual cycle and that it is influenced by the corpus luteum, of which the effect is most pronounced in the premenstrual period. He also found that there is a certain neoformation of tubules and acini before menstruation, which disappears with cessation of the periods.

There is a stimulus to growth at puberty and during the following years until the mammary glands mature. This may be so great that tumors result in the developing tissue, especially at the onset of men-

6. Mackenzie, K.: Huge Fibro-Adenoma of the Breast, Brit. J. Surg. **23**:234 (July) 1935.

7. Vos, J. J. T.: Effect of Pregnancy on Benign Tumors, Geneesk. tijdschr. v. Nederl.-Indië **73**:1497 (Nov. 21) 1933.

8. Rosenburg, A.: Ueber menstruelle, durch das Corpus luteum bedingte Mammaveränderungen, Frankfurt. Ztschr. f. Path. **27**:466. 1922.

struation (Dawson).[9] That there is a genuine hormonal effect has been shown by Watson and others, who observed that marked development of the breast may be induced by administering estrogenic substances to hypogonadal, amenorrheic girls.

It is assumed that the main factor in tumor formation is the so-called estrogenic hormone. Fibroadenoma may also arise in consequence of some ovarian dysfunction which may not be so pronounced as to produce irregularity of menstruation or disturbance in fertility. This theory is supported by the fact that fibroadenoma develops only exceptionally before puberty and rarely after the menopause. It seems, therefore, that ovarian function is essential to the development of such a tumor, although it is not necessarily the specific cause (Taylor).[3]

Diffuse virginal hypertrophy of one breast is not uncommonly accompanied by the occurrence of fibroadenoma (Geschickter) which is dependent on the duct epithelium and on the surrounding mammary tissue.

It may be said that cyclic proliferation induced by hormonal influence on certain areas is followed by incomplete regression at each cycle, which may result in tumor formation receiving fresh stimulation from each new cycle; that is, if epithelial hyperplasia takes place with faulty regression and the affected lobules undergo further proliferation at a succeeding cycle, this may result in the formation of an adenoma. If the chief fault is an overgrowth of fibrous elements exerting pressure or pull on the proliferating epithelium in the premenstruum, this may result in fibroadenoma of the ordinary intracanalicular type (Ingleby).[10]

It is possible, however, that other glands besides the ovary may influence the formation of fibroadenoma; for example, the anterior lobe of the pituitary, although this seems problematic. Gonadotropic substance from the urine of pregnant women (antuitrin S), an extract of the anterior lobe of the pituitary gland (antuitrin G) and an estrogenic substance (theelin) in combination produced a definite increase in mammary hyperplasia in rats, leading to benign fibroadenoma (Heiman and Krehbiel).[11] It is known that the ovary activated by the pituitary gland exerts a certain influence on mammary tissue. Furthermore, the anterior lobe of the pituitary and the mammary glands are certainly related (Culpepper).[12]

9. Dawson, E. K.: A Histological Study of the Normal Mamma in Relation to Tumour Growth, Edinburgh M. J. **41:**653 (Dec.) 1934.

10. Ingleby, H.: Relation of Fibro-Adenoma and Chronic Mastitis to Sexual Cycle Changes in the Breast, Arch. Path. **14:**21 (July) 1932.

11. Heiman, J., and Krehbiel, O. F.: The Influence of Hormones on Breast Hyperplasia and Tumor Growths in White Rats, Am. J. Cancer **27:**450 (July) 1936.

12. Culpepper, A. L.: Breast Tumors as Related to the Anterior Pituitary Gland, New Orleans M. & S. J. **87:**39 (July) 1934.

Lewis and Geschickter [13] found increased estrogen in patients with fibroadenoma. This was confirmed by Kahler [14] and established the power of fibroadenoma to concentrate estrogen. Recent experiments by Mohs [15] on white rats failed to show that the estrogen concentration in transplantable fibroadenoma is greater than that in surrounding tissues. Fibroadenomatous transplants develop in males and also in spayed females, though less often and less rapidly. In such cases the amount of estrogen in the body is very small; therefore, it is unlikely that estrogen is the factor stimulating to growth, and the fibroadenoma would seem to be a true neoplasm. It responds to estrogen because it derives from breast tissue. Mohs concluded that fibroadenoma in the experimental animal does not owe its growing ability to concentration of estrogen within itself.

Disturbance of the balance of hormones within the sexual cycles may be considered the most important factor in causation of fibroadenoma, but the mechanism of production still remains obscure. In a former article I expressed the view that fibroadenoma of the male breast has its inception in some hormonal disturbance at the time of puberty and senility.[2] It is interesting to note that in Menville's [16] view fibroadenoma of the male breast would be a further development of gynecomasty. I was unable to confirm this theory, as in my cases of benign fibroepithelial tumor of the male breast, I was dealing with rather localized nonencapsulated tumors without diffuse enlargement of the remaining glandular element.

Considering the different clinical and pathologic picture of fibroadenoma occurring in the male, the theory may be advanced that here the cause might possibly lie in different hormonal stimuli. Enlargement of the male breast has been observed not only in patients with atrophic testicles but also in cases of pituitary tumor (Moehlig).[17] Recently in 1 of my cases a fibroadenoma occurring in a boy aged 15 was accompanied by absence of one testicle. Further studies of the hormonal government of the breast may shed more light on the mechanism by which such a tumor is produced.

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13. Lewis, D., and Geschickter, C. F.: Estrin in High Concentration Yielded by Fibroadenoma of the Breast, J. A. M. A. **103**:1212 (Oct. 20) 1934.

14. Kahler, M. V.: The Bioassay of a Fibro-Adenoma of the Breast for Estrogenic Substance, J. Indiana M. A. **29**:374 (Aug.) 1936.

15. Mohs, F. E.: Lack of Estrin Concentration in Adenofibroma of the Mammary Gland in Rats, Am. J. Cancer **29**:356 (Feb.) 1937.

16. Menville, J. G.: Gynecomastia, Arch. Surg. **26**:1054 (June) 1933; Fatty Tissue Tumors of the Breast, Am. J. Cancer **24**:797 (Aug.) 1935.

17. Moehlig, R. C.: Pituitary Tumor Associated with Gynecomastia, Endocrinology **13**:229 (Nov.-Dec.) 1929.

From the theoretic point of view, tumor formation under hormonal influence may occur as follows:

1.—Increased sensitivity of mammary tissue to normal or nearly normal hormonal products, which may lead in some areas to more pronounced proliferation than in the rest of the tissue, regression then becoming impossible.

2.—Under the increased stimulus of hormonal dysfunction there may be glandular areas which acquire independent growth in the presence of disturbed function.

3.—Hyperconcentration of some hormonal substance may be present, which acts as an irritant, urging to growth, either on the defensive principle (connective tissue) or by excessive proliferation of the entire glandular substance.

The morphologic character of a tumor may depend on the stimulus and on the reaction of the organism. Such a reaction may take the form of control of localized growths or control may gradually break down, leading to malignant neoplasia.

As a working hypothesis it may be conceived that in the organism there are formed "mother compounds" or substances which are used by the various glandular tissues to produce hormones. If the function of the testicles or ovaries is normal, these glands will produce the amount of hormone required to maintain the function of the organism at the individual normal level. Should the sex glands be in a pathologic condition and unable to utilize the "mother compounds" to produce hormones, these compounds may possibly influence the closely related glandular structures, for example, the breast. Such dysfunction may cause excessive proliferation of the epithelial and fibrous tissues, and tumor, either benign or malignant, may result. The theory may also be suggested that the body may be refractory to the available hormones, either because it is immature (pubertal) or because it is senescent. Consequently, the breast may respond to the unused hormones, especially in the male. In the female there may be dysfunction of the ovaries not manifested clinically but producing substances which, although not estrogenic, have power to stimulate the breast tissue to tumor formation. Cystic tumors theoretically may originate in an imbalance of secretory hormones (prolactin, lutein), in addition to the *estrogenic substances* (Goldzieher).[18]

PHYSIOLOGY

It is of interest that fibroadenoma of the female breast responds to the menstrual cycle. Ingleby [10] was able to demonstrate in the tumor the same type of cyclic changes as in the adjacent normal mammary

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18. Goldzieher, M.: Personal communication to the author.

tissues and was able to determine the stage of that cycle from examination of sections of tumor, provided the menstrual cycles were regular.

It has also been found that during pregnancy there is hypertrophy of the epithelium and that during lactation the tumor is modified in a manner similar to the process going forward in the normal breast tissue (lactating adenoma: Hunter,[19] Kilgore; Kreibig; [20] Moran [21]).

Experimentally, transplanted adenoma has been shown to be influenced by the state of lactation, activity concurring at succeeding periods and involution running a parallel course. An adenoma implanted into the peritoneal cavity also shows active secretion, which one can regard as demonstrating a hormonal reaction.

Symptoms.—The chief complaint is that of a "lump." Pain is complained of in about one third of the cases and varies in character and degree. Sharp pain is only rarely noted (2 per cent) ; moderate pain occurs in 30 per cent of cases; periodical or (rarely) continuous pain, in 2 per cent. The pain is a dull local ache, stinging, pricking or burning, sometimes exaggerated immediately before, during or shortly after menstruation (4 per cent). The pain often radiates to the shoulder or arm, accompanied by sharp local pain. Exacerbation of pain may accompany rapid increase in·size of the tumor (Cheatle and Cutler [22]).

Although commonly the breasts are found to be well formed and well developed, they may be small, and one not infrequently observes fibroadenoma in the relatively small, pendulous breast. They may perhaps contain less glandular substance than the normal breast. A few are definitely underdeveloped, while some are of the virginal type of hypertrophied breast. The contour is always smooth though one breast may be larger than the other and may be deformed by a bulky tumor. It may be said that deformity caused by the new growth depends on the size of the tumor and the size of the breast, although a tumor of considerable size may be invisible in a well developed larger gland. A tumor 3 to 5 cm. in diameter may perceptibly increase the size of the breast, provided both breasts were originally of equal size.

The nipple is not retracted by the tumor but is free, although it may be thrust forward or to one side by a bulky growth. I observed no discharge from the nipple in any case in my series, but Geschickter noted this in 4 per cent of his.

19. Hunter, J. B.: Lactating Adenoma of the Breast, Proc. Roy. Soc. Med. **23**:944 (May) 1930.

20. Kreibig, W.: Ueber das Schwangerschaftsadenom der weiblichen Brustdrüse, Wien. klin. Wchnschr. **43**:972 (July 31) 1930.

21. Moran, C. S.: Fibro-Adenoma of Breast During Pregnancy and Lactation, Arch. Surg. **31**:688 (Nov.) 1935.

22. Cheatle, G. L., and Cutler, M.: Tumours of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, Philadelphia, J. B. Lippincott Company, 1931.

The skin of the gland is smooth. There is no dimpling or "pigskin" appearance, and no discoloration is perceptible unless trauma has occurred or infection is present. A large tumor may ulcerate (adenofibroma phyllodes) as a result of direct pressure, which causes local trophic disturbance.

On palpation the examiner's hand feels a firm, occasionally soft (1.1 per cent in older patients), solid or elastic (0.8 per cent), well limited, freely movable, smooth or lobulated (4 per cent) tumor.

The hardness or softness of the tumor depends on the relative amount of fibrous tissue or glandular elements present. The new growth is frequently peripheral, beneath the skin or embedded in the mammary tissue and not adherent to the skin. In my series dimpling of the skin and retraction of the nipple were observed in 3 cases (1.7 per cent), the patients' ages being 43, 43 and 19, and in these 3 cases a subsequent clinical diagnosis of malignant tumor was made. The percentage of preoperative error may, however, be higher. Buchanan[23] estimated it at 10.

The fibroadenoma may be round or oval, sometimes elongated. In size it ranges from that of a pea to that of a goose egg; it is rarely larger. In suitable cases transillumination reveals a definite shadow in 50 per cent of cases and a faint shadow in 13.8 per cent. The growth transmits light in 13.8 per cent, is indefinite in 11.2 per cent and is "negative" in 11.2 per cent. (These figures are based on my own findings.) Palpable axillary nodes were present on the same side as the tumor in 15 per cent of cases (hard nodes, 2 per cent). Soft small nodes were found in both axillas in 10 per cent. The following case illustrates the simultaneous development of fibroadenoma and carcinoma.

CASE 1.—Mrs. S. W., a white woman aged 42, a clerk, stated that for six months she had had two lumps in her right breast. Each lump when first noticed was the size of a pea, and each was gradually increasing. Both were sensitive to touch. She had had one child at 18 and had nursed it. The patient's father had died of cancer.

Clinical examination revealed markedly increased consistence of the breast. In the lower inner quadrant of the right breast was a distinctly movable mass about 2 cm. in diameter, and a similar but smaller firm tumor was observed at the lower outer quadrant of the same breast. The axillary glands were not palpable. At the request of the patient the tumor in the lower inner quadrant was removed on Nov. 27, 1931. Pathologically, the well encapsulated growth was reported as fibroadenoma. At the patient's request, the other tumor was not touched. She did not return for the regular follow-up appointments. Two years later she came in with a stony hard, somewhat nodular mass which extended from the lower outer quadrant up the entire upper outer quadrant and which cast a definite irregular shadow. There was some fixation of the nipple and adherence

23. Buchanan, E. P.: Benign Lesions of the Breast, Pennsylvania M. J. **40:** 521 (April) 1937.

of the skin. Numerous firm nodes were palpated in the right axilla. The left breast was entirely normal and transilluminated well. Roentgenograms of the chest and bones revealed no pathologic process. Radical operation for carcinoma of the right breast was performed on Nov. 28, 1933. The pathologic report was carcinoma (grade 2) of the breast and axillary lymph nodes. Healing was undisturbed, and good function of the arm was obtained. Roentgen therapy was given postoperatively. At the present time (1938) the patient is being seen in the follow-up clinic and shows no evidence of local or distant metastases.

This case emphasizes the care necessary in any consideration of so-called "harmless fibroadenoma" or cyst of the breast, and the advisability of removing any tumor so diagnosed. In fact, any lump or lumps in the breast should always be removed, and it should be the rule that frozen sections be made if the condition is at all questionable, for only pathologic examination can definitely rule out malignancy. The fact that one growth proves on removal to be fibroadenoma does not prove the like nature of any other tumor which may be present at the same time. In this case the other proved to be early carcinoma. Furthermore, in the case of malignant tumor in an early stage a timely radical operation increases the chances of permanent cure.

Pathologic Picture.—Essentially, fibroadenoma is a benign tumor presenting the structure of the mammary gland, being composed of connective tissue and glandular elements. Ewing [24] differentiated two gross forms of fibroepithelial tumor of the breast, the massive fibroadenoma and the papillary, or intracystic, fibroadenoma.

The massive fibroadenoma may be diffuse, presenting hypertrophy of neoplastic character, but most frequently the tumor is a well defined, firm fibrous mass. It may, however, be soft and vascular.

On gross inspection the growth is a round, oval or lobulated well encapsulated tumor (except fibroadenoma occurring in the male, which is diffuse) varying from microscopic size to enormous proportions. The color is usually whitish gray. The consistency depends on the structure; that is, if the tumor consists mostly of connective tissue it will be harder than if the epithelial constituents predominate or if there is underlying myxomatous or cystic degeneration. On section, whorl formation is usually seen.

Excessive development of connective tissue about the acini or ducts makes the tumor firm and more fibrous; such a tumor is called pericanalicular or intercanalicular fibroadenoma and occurs in 4 per cent of cases. When the acinic lumen is invaded by the diffuse or papillary fibrous growth the tumor is called an intracanalicular fibroadenoma (86 per cent). The two types are frequently found together in the same tumor (10 per cent of my cases).

24. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

The growth may be a villous or cauliflower-like mass covered by a fibrous capsule with an epithelial lining, which is the dilated acinus. The lining of the glandular portion is normally cuboidal epithelium. Ciliated epithelium was found in only 1 case.[25] In my series chronic cystic mastitis was an associated condition in 3 per cent of all cases and in 11 per cent of patients between the ages of 32 and 50.

It is customary to classify the tumors according to the constituent which predominates. In about 2 per cent of cases the adenomatous element exceeds the fibrous element. The tumor is therefore called adenoma. If more fibrous tissue is present with the predominating epithelial element, a tumor is formed which the pathologist calls fibroadenoma; this may be an adenofibroma if the glandular element predominates or a fibroadenoma if the fibrous tissue is in excess. It would seem sufficient, however, to use the term fibroadenoma in all instances, setting off the varieties with a qualifying adjective, such as "cellular" or "fibrous," according to which constituent is in excess. A tumor in which the acini become obliterated and compressed by the proliferating fibrous tissue to such an extent that the growth appears to be made up entirely of the latter may be confused with the rarely occurring pure fibroma, which is observed in only about 2 per cent of cases. Such a tumor may arise from the connective tissue of the skin, Cooper's suspensory ligaments or the interglandular septums of the breast. According to Beneke, fibroadenoma develops primarily from mature glandular tissue which is essentially epithelial, fibrous tissue being formed only secondarily.

Fibroadenoma may undergo benign or malignant degeneration. Benign degeneration may be cystic (which is of common occurrence) myxomatous or xanthomatous (Haagensen). Cartilaginous elements were observed in 2 cases by Cheatle and Cutler. Of far more importance is malignant degeneration, which may be carcinomatous or sarcomatous. Carcinomatous degeneration is difficult to determine and is a point much disputed. According to Junge,[26] who studied cancer of the breast, examination of the whole gland reveals simple or multiple fibroadenoma in 24 per cent of cases (25 per cent according to Cutler), which may lead to the supposition that this is a concomitant condition in a gland in which disease is generalized. One may assume that carcinoma may develop in a fibroadenoma, but it has been observed only rarely (de Quervain; Geschickter) and that it may be considered a secondary invasion (Cheatle and Cutler; Speese).

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25. Buday, K.: Proliferirendes Adenocystom der Mamma mit Flimmerepithelien, Virchows Arch. f. path. Anat. **156**:395, 1899.

26. Junge, W.: Ueber die Beziehungen zwischen der Fibrosis cystica, den gutartigen Tumoren und dem Karzinom der Brustdrüse, Beitr. z. path. Anat. u. z. allg. Path. **88**:595, 1932.

Sarcomatous degeneration, which has been definitely observed (Lörinc; Brites [22]) would seem to be of more importance. Fox [26a] stated that of his 60 collected cases of mammary sarcoma, 41 of the tumors were fibrosarcomas. Of these, 40 per cent were secondary to fibroadenoma or to intracanalicular myxoma, and the entire 57 per cent were found within the substance of a pre-existing fibroadenoma. Cheatle and Cutler stated that sarcomatous degeneration is rare. A number of quickly growing cellular tumors simulate sarcoma, but these do not metastasize.

Experimentally, Heiman and Krehbiel,[11] Oberling,[27] Guérin [28] and others observed sarcomatous degeneration of successively transplanted fibroadenoma in white rats. These were also noted by Picco after a few months of injections of an estrogenic substance.

In no case in my series of benign tumors did sarcomatous changes occur. I agree with Oliver and Major [5] that sarcomatous degeneration, though it may occur, is greatly overemphasized. The incidence of sarcoma among mammary tumors varies from 0.5 per cent (Erdmann) to 2 to 4 per cent, according to different authors. Smith and Mark found such changes in 7 per cent of 201 cases of benign tumor. The percentage in my series was 0.2.

DIFFERENTIAL DIAGNOSIS

As a rule, differential diagnosis is easy, though absolute certainty may be difficult to arrive at in certain cases, as, for example, when the freely movable, well circumscribed, firm, nonadherent growth reveals itself as a well circumscribed carcinoma. This type will be discussed in detail.

Echinococcus or cysticercus cyst of the breast is rare. Reports of single cases of actinomycosis and sporotrichosis of the mammary gland may be found in the literature (von Angerer; [29] Poteau; Quénu).

Diagnosis of maldevelopment, such as aberrant mammary tissue, gynecomasty or accessory nipple, can be readily made and need not be discussed.

Acute Inflammatory Processes.—Acute mastitis may occur in the adolescent, the newborn or the puerperant and is characterized by

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26a. Fox, S. L.: Sarcoma of Breast, with Report of 60 Cases, Am. Surg. **100:** 401 (Sept.) 1934.

27. Oberling, C.; Guérin, M., and Guérin, P.: Recherches sur des greffes en série de tumeurs mammaires benignes chez le rat, Bull. Assoc. franç. p. l'étude du cancer **22:**606 (Nov.) 1933.

28. Guérin, P.: Sarcome à cellules géantes du sein par transformation d'un fibro-adénome latent, Bull. Assoc. franç. p. l'étude du cancer **25:**326 (Feb.) 1936.

29. Angerer, H.: Geschwulstbildungen der Brustdrüse beim Manne. Deutsche Ztschr. f. Chir. **241:**104, 1933.

symptoms of inflammation. In the case of abscess the gland, which in the early stages is firm, has a tendency to resolve, or the inflammation may extend to the surface of the skin. Fluctuation is usually present.

Chronic Inflammatory Processes.—I have observed 5 cases of tuberculosis of the mammary gland. This condition may occur as simple nodules or as cold abscess with fistula. In my series there was 1 case of gumma of the breast, the diagnosis being proved by the Wassermann reaction and by subsequent antisyphilitic treatment.

Functional Disease of the Breast.—There should be no difficulty in making the diagnosis of chronic mastitis, the nodular shotty condition being diffuse and often bilateral. Neither should there be difficulty in recognizing chronic cystic mastitis (Reclus-Schimmelbusch disease), multiple cysts of the breast.

Obviously, benign tumor in the breast may arise from any of its constituent tissues. Among my cases were the following:

Lipoma.—There were 27 cases of lipoma (in 1 of which the tumor occurred in a male), comprising 3.7 per cent of all cases of benign tumor of the mammary gland and 1 per cent of all cases of pathologic conditions of the breast. Kleinschmidt's [30] figure is 2 per cent. Typically, lipoma is a lobulated fatty tumor arising in the subcutaneous fatty tissue. The intramammary and retromammary variety is frequent, and the differential diagnosis between such a tumor and a malignant tumor may be more difficult. Schneyder has described a lipoma of the female breast with total absence of the glandular element. Holland [31] found a lipoma weighing 750 Gm. in the left breast of a male patient.

Hemangioma.—The 9 cases in my series comprised 1 per cent of all cases of benign tumor of the breast and 0.3 per cent of all cases of disease of the mammary gland. Hemangioma may be a well encapsulated, elastic tumor easily excisable, although in some cases it may require extensive amputation of the breast. The simplest form is telangiectasia, but the cavernous form of tumor is most frequently observed. De Pol [32] reported a case of fibroangioma of the male breast.

Lymphangioma.—This growth is of rare occurrence. I observed 2 cases, 0.2 per cent of my cases of benign tumor of the breast and 0.07 per cent of all cases of disease of the breast. It is practically impossible to make a clinical diagnosis. Rarely lymphangioendothelioma and hemangioendothelioma may be observed.

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30. Kleinschmidt, O.: Die gutartigen Mammageschwülste, Chirurg **3**:297 (April 1) 1931.

31. Holland, T. E.: Lipoma of the Male Breast, Canad. M. A. J. **32**:74 (Jan.) 1935.

32. de Pol, G.: Fibro-angioma della mammella maschile. Policlinico (sez. chir.) **41**:679 (Dec.) 1934.

Myoma.—Those which have been observed have in every instance been leiomyoma and located in the region of the areola, originating from the smooth muscle fibers of the corium and adherent to the skin (Kleinschmidt), although cases have been reported in which the tumor was located in the breast proper (Melnick).[33]

Neurofibroma.—In my series there were 3 cases of neurofibroma (0.4 per cent of cases of benign tumor and 0.01 per cent of all cases of mammary disease).

Other tumors of extreme rarity are chondroma, teratoma (of which Coues[34] reported a case, the tumor being the size of a baseball) and xanthoma, which may be observed as a primary growth. It should be noted that fibroadenoma when it occurs in a patient with diabetes may occasionally present xanthomatous degeneration (Haagensen).[35] Neuroma of the nipple has been described by Stewart.[36]

Adenoma.—In my series there were 40 cases of adenoma, 5.5 per cent of cases of benign tumor and 1.6 per cent of all cases of mammary disease. This tumor is well defined and freely movable, moderately firm and rather elastic. Microscopic examination alone will make diagnosis certain.

Cystadenoma.—I observed 200 cases in my series, 30.4 per cent of all cases of benign tumor and 8.6 per cent of all cases of disease of the breast.[37] Cysts may be differentiated by transillumination. If the field is clear they transilluminate well. Fluctuation, if present, is only in the superficial lesion. It is usually absent, owing to tension of the fluid contents.

Fibroma.—This is a well circumscribed, hard, small tumor in the skin or gland. I observed 24 cases, 3 per cent of cases of benign tumor and 1 per cent of all cases of disease of the breast.

Papilloma.—Of this type of tumor I observed 55 instances. Three of the tumors were localized in the nipple, 23 in the skin and 26 in the duct. Three of the patients were male. Cases of papilloma comprised 7 per cent of cases of benign tumor and 2.1 per cent of all cases of disease of the breast.

33. Melnick, P. J.: Fibromyoma of the Breast, Arch. Path. **14**:794 (Dec.) 1932.

34. Coues, W. P.: A Case of Teratoma of the Breast, New England J. Med. **204**:656 (March 26) 1931.

35. Haagensen, C. D.: Xanthoma of the Breast, Am. J. Cancer **16**:1077 (Sept.) 1932.

36. Stewart, F. W.: Neuroma of the Nipple, S. Clin. North America **13**:434 (April) 1933.

37. Owing to a large number of cases, it is my intention to discuss this condition in greater detail in another paper.

Malignant Growths.—Malignant disease of the mammary gland may take the form of carcinoma, sarcoma or Paget's disease of the nipple.

1. Carcinoma: Differential diagnosis may be difficult in the case of a beginning duct carcinoma, especially if the patient is young. In a patient over 35 a solid tumor is probably a duct carcinoma, since fibroadenoma is comparatively rare at this age (Cheatle and Cutler). When the diagnosis is doubtful, careful and wide excision through the apparently healthy adjacent tissue is indicated to prevent dissemination of a possible carcinoma, and examination of frozen sections is imperative to establish the diagnosis at once. If the growth is malignant, radical mastectomy is done immediately.

When the classic picture of carcinoma is absent, the diagnosis, even when made by experienced observers, carries a factor of error of 3 per cent. Cases in which the growth simulates fibroadenoma comprise about 2 per cent. Yet in cases of this type a correct diagnosis at this early stage is of the greatest importance, since early radical mastectomy increases the chances for permanent cure. Palpable axillary lymph nodes, especially if hard, suggest carcinoma.

The following cases are illustrative:

CASE 2.—Mrs. C. R., a white woman aged 43, came to the tumor clinic of the Skin and Cancer Unit on June 3, 1933, for treatment of a small lump in her right breast, which she had noticed the week before. She stated that pain had led to its discovery. She had nursed each of her two children for about nine months, the last one ten years previously. The menstrual history was normal and the medical history noncontributory. The patient's father had died of carcinoma of the throat. The patient was a well developed and well nourished woman with pendulous, apparently normal breasts presenting no change in contour of the nipple. In the upper outer quadrant at the periphery of the right breast, about 6 cm. distant from the nipple, was a firm, freely movable nontender nodule measuring 1 cm. in diameter. The axillary glands were not palpable. A diagnosis of fibroadenoma was made, and excision was undertaken. At operation the tumor was found to be slightly adherent to the surrounding tissues. It was gritty and diffuse, and carcinoma was suspected by the operator. Frozen sections confirmed this suspicion, and radical mastectomy was immediately performed. The pathologist reported scirrhous carcinoma, grade 2, with hyperplasia of the axillary lymph glands. The patient was seen in the follow-up clinic four years later. She was in good condition and free of recurrence.

CASE 3.—Mrs. H. H., a white woman aged 38, applied for treatment on Oct. 28, 1931, stating that eighteen months previously she had discovered a small lump in her right breast. Her family physician, whom she had consulted six months previously, did not advise its removal, saying it was benign. The patient had one child, then 14 months old. There was no history of miscarriage. Her sister had a tumor of the breast, of unknown nature. The patient was a well developed and well nourished woman with normal breasts of medium size, showing no change in shape or contour. The nipples were prominent and freely movable. In the upper outer quadrant of the left breast, about 5 cm. from the nipple, was an

irregular, nodular firm mass about 1 cm. in diameter. It was not attached to the skin. There were no enlarged lymph nodes in the corresponding axilla. A diagnosis of fibroadenoma was made, and removal of the growth was advised. The patient postponed the operation and did not return to the clinic for eighteen months. On her return after this lapse of time the tumor was found to have increased to a diameter of 4.5 cm. It was attached to the skin with puckering of the surrounding skin and cast a definite shadow by transillumination. There were five firm lymph nodes in the left axilla. The case presented the classic picture of carcinoma of the breast with metastasis to the regional lymph nodes. Radical operation was performed in March 1933. Pathologic examination revealed medullary carcinoma, grade 2, with maxillary metastasis. Two years later, in spite of roentgen therapy instituted after operation, generalized metastases with jaundice and other symptoms developed, and the patient died forty-six months after the operation.

When this type of case is considered it is clear that tumor of the breast occurring in patients past the age of 35 should be considered carcinoma until proved otherwise by frozen section and should be treated accordingly.

2. Sarcoma: In its early stages sarcoma may stimulate benign fibroepithelial tumór, but its unusually quick progressive growth soon arouses suspicion. There were 2 such cases in my series.

TREATMENT

Until better knowledge of the physiologic and pathologic character of the lesion is at hand and until prevention of such growth may be accomplished with the aid of endocrinology, surgical removal remains the only form of treatment. All solid tumors of the mammary gland should be removed, regardless of the patient's age or sex. Such removal is imperative not only to relieve the patient's mind but also because only such removal, supported by pathologic examination, can rule out malignancy. In the second and third decades of life malignant lesions of the breast are rare but they occur, and this fact makes removal the wise course.

The technic employed is a matter of choice, ranging from a simple radial incision, preferably with the patient under general anesthesia, to an esthetic circular incision in the fold of the breast or encircling the areola. Only exceptionally should the growth be enucleated; this may be done, however, for a small, superficial tumor. As a general thing it is recommended that the growth be excised together with the corresponding sector of the breast, in order properly to eradicate the lesion and prevent recurrence. Mastectomy may be necessary in the case of a large, bulky tumor.

Postoperative Results.—Wix[38] reported that after removal of the fibroadenoma 66 per cent of patients had no further complaint, but 34

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38. Wix, W.: Das Schicksal der gutartigen, nicht entzündlichen Mamma-erkrankungen, speziell der chronischen Mastopathie und des Fibroadenoms, Thesis, Kiel, 1932.

per cent did complain, and of these 21 per cent had pain in the breast which had not been operated on. The pain coincided with menstruation but probably had no relation to it.

Recurrence took place in 3.5 per cent of my cases. Wix reported recurrence in 8 per cent, Lamb in 2 per cent and Geschickter in 10 per cent.

SUMMARY AND CONCLUSIONS

A statistical study is presented of 722 cases of benign tumor of the breast, with a particular discussion of 270 fibroadenomas of the female breast.

Fibroadenoma is a benign tumor which develops shortly after puberty. Such a tumor may arise as a result of disturbance of the endocrine secretory function or of related functions.

Fibroadenoma of the breast in the female, contrary to that occurring in the male, is well encapsulated, freely movable, firm, solid and rarely attached to the skin and surrounding tissues. Exceptionally, it may suggest a malignant growth.

Malignant degeneration did not take place in any of my cases, and its occurrence is doubtful.

Differentially, the greatest risk of error lies in the possible presence of certain types of carcinoma which may simulate fibroadenoma. Certainty can be obtained only by microscopic examination.

It is of interest and importance that benign tumors outnumber malignant tumors in a ratio of approximately 2:1.

The treatment is surgical excision.

ANOMALOUS FIXATION OF THE MESENTERY

REPORT OF TWO CASES

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Anomalous fixation of the mesentery occurs fairly often. It varies from the rare primitive forms of embryonic fixation associated with nonrotation of the intestines to the common late forms of nonattachment of the mesentery of the ascending colon. Often no symptoms result, but sometimes symptoms arise owing to abnormal mobility of the ascending colon or to complications resulting from the mesenteric anomalies. Among possible complications caused by such anomalies are: intestinal obstruction caused by volvulus, intussusception or so-called internal hernia; obstruction caused by congenital peritoneal bands, and such complications as may arise from misplacement of the cecum and of the appendix.

The anomalies encountered after birth are believed to be due to arrests in fetal development. They fall naturally into one of the three stages into which fetal development has been divided by Frazer and Robbins,[1] by Dott [2] and by others. The present report deals only with the last of these stages.

Anomalies resulting from arrests in the third stage of intestinal development are more common than anomalies of the first or the second stage. They are, however, less striking. because they are characterized by a normal adult sequence of viscera, the intestines having fully developed and fully rotated; the resulting anomaly is simply one of failure of mesenteric adhesion to the posterior parietes. Anomalies of the third stage, moreover, are less likely to produce symptoms or complications necessitating surgical treatment. Consequently, they have received less consideration in the literature than have anomalies of the first and the second stages.

To appreciate the significance of such anomalies it is necessary to recall the course of intestinal development of the human fetus. This occurs. according to Frazer and Robbins [1] and Dott,[2] as follows: The primitive gut is divided by its blood supply into three parts. namely, the foregut. the midgut and the hindgut. The foregut is

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1. Frazer, J. E.. and Robbins, R. H.: On the Factors Concerned in Causing Rotation of the Intestine in Man, J. Anat. & Physiol. **1**:75-110, 1915.

2. Dott, N. M.: Anomalies of Intestinal Rotation: Their Embryology and Surgical Aspects, with Report of Five Cases. Brit. J. Surg. **11**:251-286, 1923.

supplied by the vessels of the celiac axis and comprises the stomach and the duodenum. The midgut is supplied by the superior mesenteric artery and comprises the entire small intestine, together with the cecum, the appendix, the ascending colon and the transverse colon as far as its middle third. The hindgut is supplied by the inferior mesenteric artery and comprises the remainder of the transverse colon together with the distal part of the colon as far as the anal canal.

The midgut, because of its complex mode of evolution, is responsible for many developmental anomalies. It progresses, according to Dott, through three stages of rotation. The first stage of rotation occurs about the eighth week of development of the human embryo. The midgut, already possessing a mesentery with sagittal fixation of the root, is still attached to the yolk sac at the vitelline duct and protrudes through the umbilicus. It begins to rotate counterclockwise with the superior mesenteric artery as an axis, owing to the pressure of the left umbilical vein.

In the second stage of rotation the small intestine returns into the abdomen, posterior to the superior mesenteric vessels. Rotation occurs through an arc of 270 degrees in counterclockwise direction until the normal adult intestinal sequence has been attained. The cecum is the last part of the midgut to return to the abdominal cavity.

At the beginning of the third stage the intestinal sequence is the same as in the adult, but the cecum still lies high. Moreover, the midgut is still attached to a large common mesentery with a small root. During the third stage the cecum descends into the right lower quadrant of the abdomen, and the mesentery of the ascending colon adheres to the posterior parietes as far as the line of the superior mesenteric artery, thus forming the normal adult mesenteric root for the small intestines. The third stage occurs in the human embryo of about 63 mm., or at about the twelfth week of embryonic growth.

The hindgut retains some of its primitive mesentery until the third stage of development, during which the mesentery of the descending colon adheres to the posterior parietes.

Two instances of anomaly of the third stage of development were recently observed in cadavers. They were accidentally encountered during the routine dissection of 148 successive cadavers by students and instructors in the department of anatomy under the direction of Dr. Robert J. Terry.

REPORT OF CASES

CASE 1.—The cadaver was that of a Rumanian man who died in St. Louis City Hospital No. 1 on Nov. 3, 1930, at the age of 60. Death was due to chronic myocarditis and hypostatic bronchopneumonia. Dissection was performed in November 1931. The body was preserved by injection into the right femoral artery of solution of formaldehyde U. S. P. in a 10 per cent concentration. The state of preservation of the cadaver at the time of dissection was excellent. There was

no history of previous abdominal illness. There had been no operations, and the abdominal wall showed no scar. During the stay in the hospital the intake of food and fluid and the output of feces were in no way abnormal.

Figure 1 shows the viscera of the cadaver. For the drawing the mesentery was viewed from below. The small intestines and the right side of the colon possessed a common mesentery. The mesentery had a small root which was

Fig. 1.—Mobile cecum and intestines. The mobility resulted from faulty mesenteric fixation during the third stage of intestinal rotation. *D*, duodenum; *G Bl*, gallbladder. The arrow disappears into the epiploic foramen.

coextensive with the superior mesenteric artery. The superior mesenteric artery lay anterior to the third portion of the duodenum. The third portion and part of the second portion of the duodenum lay within the mesentery, as did the head of the pancreas. The mesentery was continuous with the mesentery of the transverse colon.

The right colic (hepatic) flexure was held to the gallbladder and the liver by peritoneal bands. The left side of the colon was unaltered, and the descending colon had no mesentery.

The attachment of the right colic (hepatic) flexure was interesting. Figure 2 shows the origin of a congenital peritoneal band from the inferior surface of the quadrate lobe of the liver, extending thence to the right colic flexure. The right colic flexure was supported by this congenital band. Additional support was furnished by adhesions between it and the gallbladder, which may not have been of congenital origin.

The hepatocolic ligament of this cadaver was thin and resembled peritoneum. It was about 5 cm. in width. It resembled certain accessory ligaments which are common in this region and which, according to Cole,[3] Wakefield and Mayo[4] and others, are of congenital origin.

Fig. 2.—At *H* is shown the attachment to the liver of a congenital ligament running to the right colic flexure.

Had it not been for this method of fixation of the right colic flexure, the whole of the midgut of this cadaver would have hung from a small pedicle at the superior mesenteric artery and would have been especially liable to volvulus.

Figure 3 shows diagrammatically the peritoneal reflections of the posterior abdominal wall in this cadaver. The root of the mesentery lay at the level of the upper border of the body of the second lumbar vertebra. It was continuous above with the mesentery of the transverse colon, which was arranged

3. Cole, W. H.: Congenital Malformations of the Intestinal Tract and Bile Ducts in Infancy and Childhood, Arch. Surg. **23**:820-847 (Nov.) *1931.*

4. Wakefield, E. G., and Mayo, C. W.: Intestinal Obstruction Produced by Mesenteric Bands in Association with Failure of Intestinal Rotation, Arch. Surg. **33**:47-67 (July) 1936.

in normal fashion. The descending colon was fixed to the posterior parietes in the usual fashion. The sigmoid flexure possessed a normal mesentery, and the relations of the rectum to the surrounding structures were unaltered. The omentum was normal. The vascular system of the abdomen was normal.

The cadaver showed several associated anatomic anomalies. The frontal bone possessed one metropic suture. There were double hypoglossal canals on both sides. The xiphoid process was bifurcate. The fifth lumbar vertebra showed separation of the inferior articular processes. Each femur had a large trochanter tertius. The second and third phalanges of the little toes of both feet were fused.
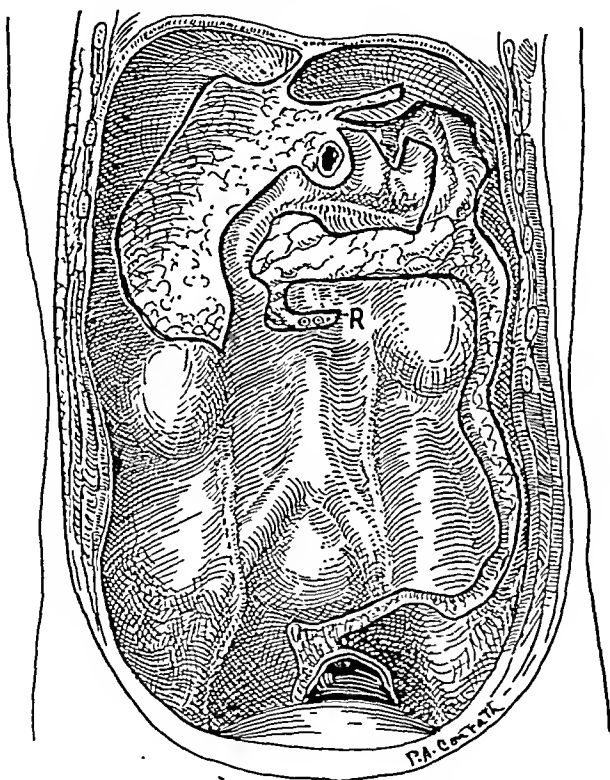
Fig. 3.—Semidiagrammatic drawing of the mesenteric root after removal of the preperitoneal viscera. *R*, root of the mesentery of the duodenum, the small intestines and the ascending colon. The root contains the superior mesenteric vessels and lies over the pancreas.

CASE 2.—The cadaver was that of Mrs. M. R., a Negress aged 41, who died at St. Louis City Hospital No. 2 on Feb. 24, 1932, of carcinoma of the cervix uteri, complicated by pulmonary tuberculosis. There was nothing in the history of this patient to suggest congenital abdominal disease, and there were no abdominal scars. Dissection of this cadaver was performed in February 1933. The cadaver was preserved in solution of formaldehyde by a technic similar to that used with the previous cadaver. It was in good condition for dissection.

The cadaver possessed a primitive mesentery almost identical with that just described except that the right colic flexure was not attached to the liver. The

superior mesenteric artery lay anterior to the third part of the duodenum, at the level of the body of the second lumbar vertebra. Associated anomalies observed in this cadaver were as follows: (1) The posterior arch of the atlas was not united; (2) there were no parietal foramens in the calvaria; (3) the left humerus possessed an intercondylar foramen, and (4) the second and third phalanges of both little toes were fused.

<div align="center">COMMENT</div>

Incidence.—These 2 cases illustrating failure of mesenteric fixation during the third stage of intestinal development were encountered in the course of dissection of 148 successive cadavers. The incidence of the anomaly in the series of dissections was 1.4 per cent. Treves [5] observed 2 similar anomalies during dissection of 100 bodies immediately post mortem, an incidence of 2 per cent. Waugh [6] reported a 20 per cent incidence of mesenteric anomalies in a series of several hundred autopsies on children under 12. However, all types of intestinal anomalies which caused mobility of the ascending colon were included in his series. Moritz [7] stated that "secondary attachments (of the mesentery) are incomplete in almost 25 per cent of all individuals."

Cause.—It is possible that certain mechanical forces may cause failure of mesenteric adhesion to the posterior parietes in the third stage of rotation. It was interesting to find in the cadaver in the first case a hepatocolic ligament which served to support the hepatic flexure of the colon and acted as an anchor for the entire mesentery. This ligament was believed to be of congenital origin. It resembled a congenital band which extended from the transverse fissure of the liver over the gallbladder and the second portion of the duodenum to the hepatic flexure in a case reported by Waugh.[8]

Congenital bands in the neighborhood of the duodenum are not uncommon. They were first described by Virchow in 1853, according to Wakefield and Mayo, and have been studied by Garnier and Villemin,[9] Latarjet and Tavernier [10] and others. They have been found associated

5. Treves, F.: The Anatomy of the Intestinal Canal and Peritoneum in Man, London, H. K. Lewis, 1885; Clinical Lecture on Hernia into the Foramen of Winslow, Lancet **2**:701, 1888.

6. Waugh, G. E.: The Morbid Consequences of a Mobile Ascending Colon with a Record of One Hundred and Eighty Operations, Brit. J. Surg. **7**:343-383, 1920.

7. Moritz, A. R.: Mesenterium Commune with Intestinal Obstruction, Am. J. Path. **8**:735-744, 1932; Developmental Anomalies Causing or Predisposing to Intestinal Obstruction, Ohio State M. J. **30**:429-433, 1934.

8. Waugh, G. E.: Congenital Malformations of the Mesentery: A Clinical Entity, Brit. J. Surg. **15**:438-449, 1928.

9. Garnier, C., and Villemin, F.: Ligaments hépatiques accessoires chez le foetus humain, Bibliog. anat. **20**:80-92, 1910.

10. Latarjet, A., and Tavernier, L.: Un cas de defaut d'accolement du mesentère primitif dans le territoire irrigué par l'artere mesenterique superieure, Bibliog. anat. **20**:93-96, 1910.

with failure of mesenteric adhesion to the posterior parietes with sufficient frequency to raise the question whether they may not be a cause of such failure. Cole concluded that congenital bands in the region of the duodenum are caused by incomplete absorption of the stem processes that support the liver and pancreas as they bud forth from the duodenum early in embryonic life. It is possible that such congenital bands may sometimes give enough mechanical support to the right side of the colon to prevent its full fixation to the posterior abdominal wall.

Another anomaly associated with failure of mesenteric adhesion in the third stage of intestinal rotation was the occurrence of a congenital foramen in the mesentery of the small intestine in a case reported by Moritz.[7]

Symptoms.—Waugh claimed that a mobile ascending colon often gives rise to symptoms and reported 180 operations for the cure of the condition. His work does not appear to have received confirmation, and an unusually mobile cecum is not generally thought to cause symptoms or to require surgical fixation.

Signs.—No abdominal physical signs arise from this type of anomaly per se. Such signs as may arise are due to the consequences of the anomaly, namely, to a malplaced appendix to volvulus or to intestinal obstruction. A diagnosis by roentgen examination is possible. The right half of the colon may be seen to gravitate to the right or to the left of the abdomen, according to the position of the patient and the manipulation of the right half of the colon. If normal adult sequence of intestines is not present the anomaly is probably one of the first or second stage, not the third.

Diagnosis.—At operation it is of more than theoretic importance to recognize this anomaly. The diagnostic point is the relation of the duodenum to the superior mesenteric artery. If the duodenum lies posterior to the artery in the presence of deficient mesenteric fixation, the anomaly is one of the third stage of development, because counterclockwise rotation of the intestines through an arc of 270 degrees has occurred in normal fashion. However, if the duodenum lies anterior to the superior mesenteric artery the anomaly is one which has resulted from defective rotation in the second or the first stage, and the normal adult sequence of intestines cannot be expected. These points are of practical importance in the reduction of volvulus which may have occurred from an intestinal anomaly. Volvulus always occurs in clockwise direction.

Roentgen diagnosis of anomalies of intestinal rotation has been discussed by Rubin.[11]

11. Rubin, E. L.: Radiological Aspects of Anomalies of Intestinal Rotation. Lancet 2:1222-1226, 1935.

Sequelae.—Failure of mesenteric adhesion in the third stage of rotation results in a freely movable cecum, or cecum mobile. It is possible, in consequence of this mobility, for the appendix to migrate to any quadrant of the abdomen. The potentialities in the nature of atypically located appendicitis are obvious.

Cases in which the anomaly has resulted in intestinal obstruction have been recorded by Moritz. In 1 of his cases the obstruction was due to a volvulus of the small intestine and the right half of the colon about the superior mesenteric artery. The result was obstruction at the third portion of the duodenum, and the patient died after the operation, not from this obstruction but from another unrelieved obstruction of the small intestine in a congenital foramen in the mesentery, not recognized at the time of the original operation. Ladd [12] has discussed duodenal obstruction in infancy and in childhood caused by this and by other anomalies. Another patient of Moritz' had intussusception of the terminal part of the ileum into the cecum as a result of the anomaly.

In 3 cases reported by Pratt and Fallis [13] the patients had intestinal obstruction from cecum mobile.

Anomalies of the third stage of intestinal rotation seem to be well tolerated and to be associated with relatively few morbid sequelae. Morbid sequelae occur much more often from anomalies of the first and second stage of intestinal rotation. The articles of Haymond and Dragstedt [14] and of Gardner and Hart [15] summarized the present status of these anomalies.

SUMMARY

Two cases illustrating developmental anomalies of the third stage of intestinal rotation are presented. Apparently neither anomaly caused symptoms during life, and both were discovered accidentally post mortem, during routine dissection. The 2 cases were observed in the course of dissection of 148 successive cadavers.

Evidence is presented to confirm the belief that this type of anomaly occurs in over 1 per cent of adults. It is probably unrecognized as a rule because it fails to cause symptoms. Owing to its presence, however, the cecum becomes mobile and the appendix becomes liable to malposition. Sequelae, i. e., different forms of intestinal obstruction, have been reported.

12. Ladd, W. E.: Congenital Obstruction of the Duodenum in Childhood, New England J. Med. **206**:277-283, 1932.

13. Pratt, J. P., and Fallis, L. S.: Volvulus of the Cecum and Ascending Colon: Report of Three Cases, J. A. M. A. **89**:1225-1230 (Oct. 8) 1927.

14. Haymond, H. E., and Dragstedt, L. R.: Anomalies of Intestinal Rotation: A Review of the Literature with Report of Two Cases, Surg., Gynec. & Obst. **53**: 316-329, 1931.

15. Gardner, C. E., Jr., and Hart, D.: Anomalies of Intestinal Rotation as a Cause of Intestinal Obstruction, Arch. Surg. **29**:942-981 (Dec.) 1934.

PRIMARY CARCINOMA OF THE NAIL

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AND

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Neoplasm arising from the nail is one of the rarest manifestations of malignant disease. A careful search of the literature reveals only 17 proved cases and 1 probable case. Carcinoma of the nail develops, according to Pardo-Castello,[1] from the epithelium of the bed, the matrix or the nail grooves and is usually of the prickle cell type. An additional case is here reported.

REPORT OF CASE

A white man aged 65 came to the outpatient department of the City Hospital on May 25, 1936, complaining of pain in the left great toe. The nail along the mesial side resembled an ingrowing nail and was treated accordingly but failed to improve. Three weeks later part of the nail was removed, and a warty growth beneath it was revealed. Eleven days later, block anesthesia being employed, the mass was further exposed and apparently entirely removed. The tissue was not submitted for histologic examination. Pain persisted and was accompanied by swelling, redness and tenderness. On August 28 an abscess-like cavity was present which could be probed to the bone. The discharge was described at various times as sebaceous or caseous. Roentgen examination showed lateral hypertrophic exostosis and destruction of the terminal phalangeal bone. A diagnosis of chronic osteomyelitis was made, and the patient was admitted to the hospital on September 10. Five days later the distal phalanx was amputated through the interphalangeal joint.

The pathologic report stated: "The specimen consists of a left great toe amputated through the interphalangeal joint. The nail had been cut diagonally, exposing the mesial portion of the subungual tissue, which appears heaped up and granular. On sagittal section of the toe, an ovoid mass near the tip is noted, immediately beneath and connected with the nail bed. This mass measures 1.5 cm. in length and 1 cm. in width. It grows toward the plantar surface and has destroyed the tip of the bone of the distal phalanx. It is firm, elastic, white and well demarcated from the surrounding tissue. The nail appears thicker than normal.

"Histologic structure: The tumor mass grows down from the nail bed and is formed by the coalescence of long pegs of squamous epithelium. Toward the center the cells are large polyhedral cells, sometimes flattened into platelike structures. The nuclei here are relatively small and vesicular. There is a definite tendency to intraepithelial keratinization, and some typical epithelial pearls are present. Intercellular bridges are prominent. Many foci are rich in keratohyaline granules. At the periphery of the mass the cells are compressed and are smaller

1. Pardo-Castello, V.: Diseases of the Nail, Springfield, Ill., Charles C. Thomas, Publisher, 1936, pp. 47-50.

than toward the center. The nuclei are fairly large and moderately hyperchromatic, with fairly large nucleoli, and there is an occasional mitotic figure. In a few areas there is destruction of the basal limiting membrane, and isolated epithelial
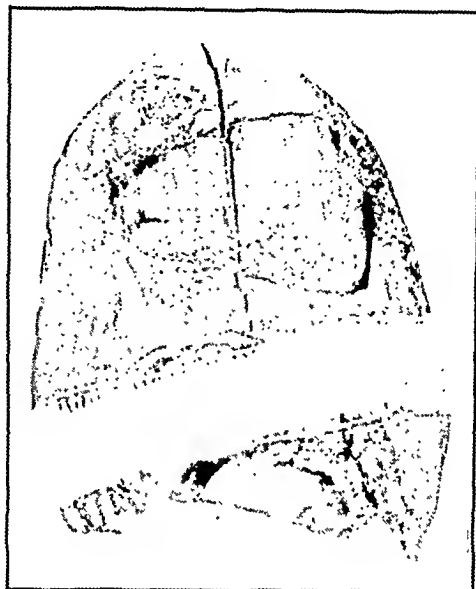

Fig. 1.—Amputated toe, showing the granular appearance of the subungual tissue revealed by partial removal of the nail.
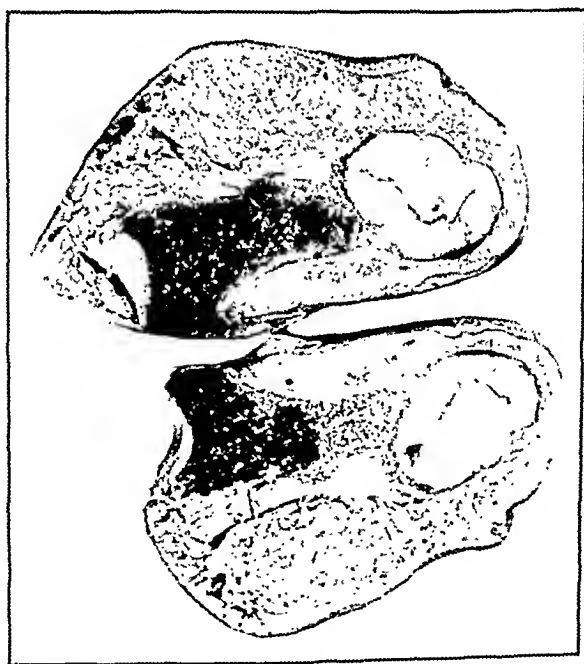

Fig. 2.—Sagittal section of the toe. The tumor mass has grown down from the under surface of the thickened nail and has destroyed the tip of the phalangeal bone.

cells are present in the adjacent connective tissue. The central portion of the tumor has large defects which communicate with the heaped-up granular area noted on the surface of the gross specimen. This area is similar to the main tumor mass, and some portions show a definite transition to nail-plate cells.

"Near the edge of the tumor the epithelium of the nail bed becomes increasingly acanthotic. In the corium there is dense infiltration with small round cells, plasma and lymphoid cells predominating in different foci. There is a scattering of eosinophilic cells. The tumor mass has destroyed by pressure the tip of the phalangeal bone. The periosteum adjacent to the tumor shows slight productive changes, and the underlying marrow spaces are fibrotic. Some young osteoid lamellae are being formed. The majority of the bone shows osteoporosis. Malignant cells have not invaded the bone itself.

"The diagnosis is primary squamous cell carcinoma of the nail of the left great toe, originating from the nail bed."
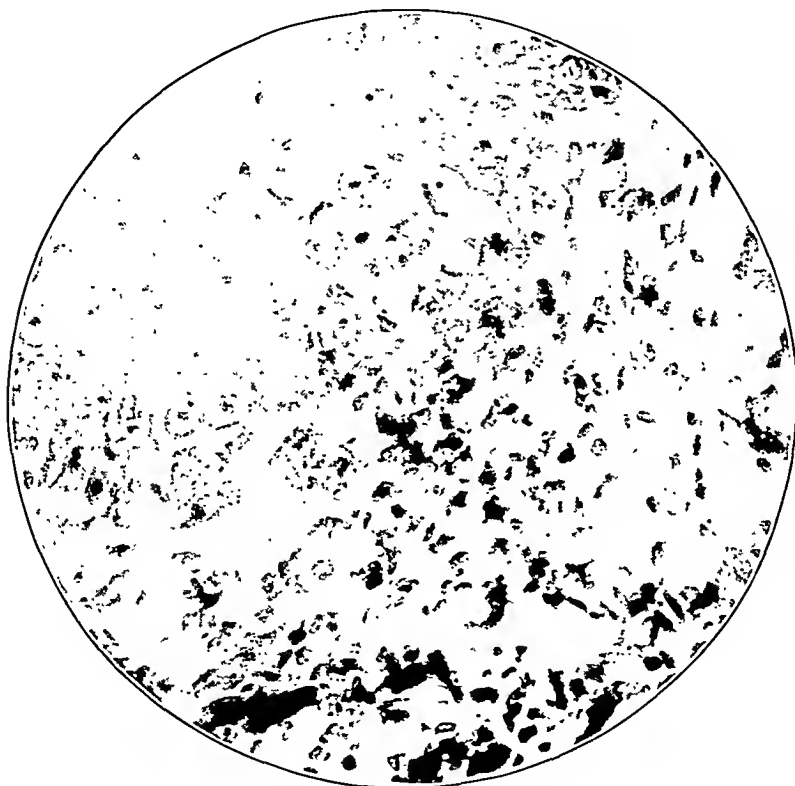
Fig. 3.—High power photomicrograph of the edge of the tumor, showing local invasion by malignant epithelial cells. There is dense small round cell infiltration.

COMMENT

The accompanying table summarizes the salient features of the previously reported cases. In the total 19 cases (including our own), 11 patients were males, 7 were females and the sex of 1 was not noted. The ages varied from 21 to 75. Ten of the patients had a definite history of injury, often followed by chronic infection, preceding the frank development of malignant tumor. The period from the time of injury to the time malignant tumor was diagnosed was given in some cases and

Previously Reported Cases of Primary Carcinoma of the Nail

Case Number and Author	Sex	Age	Antecedent Condition	Injury	Duration*	Site	Treatment	Result	Histologic Structure
1. Velpeau, M.: Gaz. d. hôp. 2:311, 1850	F	61	Occupational use of chemical solutions for several years	Puncture wound	1 yr.	Right index finger	Amputation	Cure	Epithelioma
2. Küster	M	34	Ingrowing nail	Injury followed by chronic paronychia	6 mo.	Right thumb	Amputation	Cure	Squamous cell carcinoma
3. Lücke, cited by Rokoch, C.: Ueber die chirurgischen Affektionen des Nagelfelds, Thesis, Bonn, 1889	M	65	None	Yes	.....	Right thumb	Amputation	Cure	Carcinoma
4. Robin: Bull. Soc. anat. de Paris 48:12, 1873	F	21	None	None	.....	Right index finger	Amputation	Cure	Epithelioma
5. Krönlein	M	44	None	Crushing injury followed by painful scar	11 yr.	Right little toe	Amputation	Died†	Carcinoma
6. Hutchinson		70	Purulent discharge	None	1 yr.	Thumb	Amputation	Cure	Epithelioma
7. Tourel: Bull. Soc. anat. de Paris 64:30, 1889	M	35	Ingrowing nail with chronic paronychia	None	.....	Great toe	Amputation	4 yr. cure	Epithelioma
8. Kölliker, cited by Volkmann: Samml. klin. Vortr., 1890 (Chir. no. 162), p. 323			.....	.....	.....	Great toe	Amputation	Cure	Carcinoma
9. Peyrot, cited by Heller, J.: Diseases of the Nails, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 13, pt. 2, p. 188	F	48	.....	.....	10 yr.	Right index finger	Amputation	.....	Carcinoma
10. Blakeway, H.: St. Barth. Hosp. Rep. 46:193, 1910	M	50	Loose nail and purulent discharge	None	.....	Right thumb	Amputation	Cure	Squamous cell carcinoma
11. Heidingsfeld, M. L.: Lancet-Clinic 113:383, 1915	M	60	None	Injury followed by indolent ulcer	1 yr.	Right thumb	Amputation	.....	Clinical diagnosis of epithelioma; no histologic exam.
12. Chajes	M	60	None	Yes	10 yr.	Right index finger	Amputation	.....	Carcinoma
13. Eisenklam, D.: Wien. klin. Wchnschr. 44:1102, 1931	F	20	.....	.....	18 yr.	Right thumb	Refused	.....	Papilloma with early malignancy
14. Eisenklam	M	50	.....	Yes	10 yr.	Right thumb	Radium	Cure	Basal cell carcinoma
15. Riechon and others: Bull. et mém. Soc. de radiol. méd. de France 20:232, 1932	M	66	.....	.....	.....	Right great toe / Left great toe	.....	Cure	Basal cell carcinoma
16. Silverman, I.: Am. J. Surg. 20:141, 1933	F	70	Puncture wound under nail	.....	.....	Middle finger	Removal of nail	Cure	Squamous cell epithelioma
17. Pardo-Castello	M	50	Injury followed by chronic paronychia	Splinter under nail; suppuration 3 years later	2½ yr.	Right thumb	Removal of nail / Radium	Local recurrence Cure	Prickle cell epithelioma
18. Pardo-Castello	F	73	Bowen's disease	.....	4 yr.	Thumb	Roentgen therapy / Radium	Cure	Prickle cell epithelioma

* Time given is between onset of symptoms and time of diagnosis.

† Metastases to inguinal lymph nodes, gangrene of leg and death following surgical removal of nodes.

varied from six months to eighteen years. The type of trauma, infrequently noted, was in 3 cases a deep puncture wound between the nail and the nail bed; in 1 case it was a crushing injury.[2] Infection, when present, was resistant to treatment. In 3 cases the carcinoma followed paronychia. In 2 of these cases paronychia followed injury, and in 1 of these there was an ingrowing nail; an ingrowing nail was also present in the case of nontraumatic paronychia. In 1 case the carcinoma followed Bowen's disease, a condition sometimes considered precancerous. The history of trauma seems to explain the sites of predilection; the lesions occurred in those parts which are most subject to injury. Thus, in 13 cases the hand was affected, and in 9 of these the diseased digit was the right thumb or index finger. Of the 6 tumors involving the foot, all were on either the great or the small toe.

Pain was noted as a prominent symptom in 7 cases. From the slowly expanding nature of the lesion and its limitation by the rigid nail and by phalangeal bone it seems probable that pain was present in some of the other cases also.

In the case here reported there was a discharge described as sebaceous or caseous. This probably represented an actual discharge of cancer tissue and might have been of some diagnostic value.

The most frequent histologic diagnosis was squamous cell carcinoma. There were 2 cases of basal cell carcinoma and 1 of papilloma with early malignant degeneration. Pardo-Castello stated that carcinomas of the nail are rather malignant, but in our review of the cases the malignancy appears to be of a low grade. In only 4 cases, including our own, was mention made of the presence or absence of involvement of bone. In 1 case[3] there was no involvement of the bone. In our own case and 1 other[4] there were erosion and atrophy of bone, caused by pressure rather than by invasion. In only 1 case[5] was there true local invasion of bone. Metastases from carcinoma of the nail are infrequent, if one may so infer from the fact that they are seldom mentioned. In a single instance only were the draining lymph nodes involved.

The treatment has been amputation, excision of the nail and radium or roentgen therapy. The results seem to have been uniformly good, except for 1 case in which there were metastases to the lymph nodes and 1 case of local recurrence after administration of roentgen therapy.

2. Krönlein, R. W.: Langenbeck'sche Klinik und Poliklinik zu Berlin: Extremitäten; Geschwülste, Arch. f. klin. Chir. (supp.) **21**:336, 1877.

3. Küster, E.: Chirurgisch-onkologische Erfahrungen, Arch. f. klin. Chir. **12**:629, 1871.

4. Hutchinson, J., Jr.: Epithelioma of the Nail, Tr. Path. Soc. London **36**:468, 1885.

5. Chagas, C. P.: Carcinoma of the Matrix of the Nail of the Great Toe, Brasil-med. **35**:233, 1921.

SUMMARY AND CONCLUSIONS

The literature on carcinoma of the nail is reviewed, and an additional case is reported. Many of the neoplasms develop after trauma followed by chronic infection. The site of predilection corresponds with the fingers and toes most subject to injury, the right index finger and thumb and the great and little toe. The neoplasm usually is a squamous cell carcinoma and is of a low grade of malignancy. Local recurrence and metastases are very infrequent. Cure usually results from amputation or radium therapy.

A PLASTIC OPERATION ON THE BREAST

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Plastic operation on the breast is a recent addition to plastic surgery. This new field owes some of its demand to the importance that women of today attribute to a properly proportioned form. Vogues and sports have given rise to comparisons which make a woman conscious of having a normal or an abnormal form. Therefore, hypertrophic and pendulous breasts, which in moderate degrees are fairly common, may constitute a psychic handicap. For a small group of women with enormously heavy breasts, there is added to the psychic handicap a physical one, and the two may constitute a tragedy of life, since they frequently occur in young women with otherwise slim figures. When it is possible safely and satisfactorily to correct a deformity of the breasts and thus to restore the happiness of a patient, plastic reconstruction of the breast is a justifiable operation.

Surgeons distinguish an atrophic pendulous breast from a hypertrophic one. In the former, the breast is a flabby sac of skin containing scanty breast tissue at its bottom. In the hypertrophic form, the enlargement of the breast is due to overdevelopment of its tissue and consists of glandular tissue and fat.

The reconstructive operation for a pendulous breast has a twofold purpose: first, that of correcting the deformity and, secondly, that of maintaining the function of the gland. To accomplish these aims, several operative methods, which have recently been described by Maliniak [1] and by Biesenberger,[2] have been devised. Biesenberger has divided the different operations into four groups—partial amputation, mastopexy, dermatoplasty and dermatoplasty plus resection. The first method is performed nowadays only in exceptional cases, since it is always combined with a separation of the nipples from the glandular tissue and therefore with loss of function. Mastopexy and the various

1. Maliniak, J. W.: Pendulous Hypertrophic Breast, Arch. Surg. **31**:587 (Oct.) 1935.

2. Biesenberger, H.: Deformitäten und kosmetische Operationen der weiblichen Brust, Vienna, Wilhelm Maudrich, 1931.

methods of dermatoplasty have a limited scope, as they do not decrease the size of the breasts. When the operation of resection and displacement of the nipples to their natural places was devised, however, a reliable method was afforded of reconstructing pendulous breasts into natural forms without disturbing function.
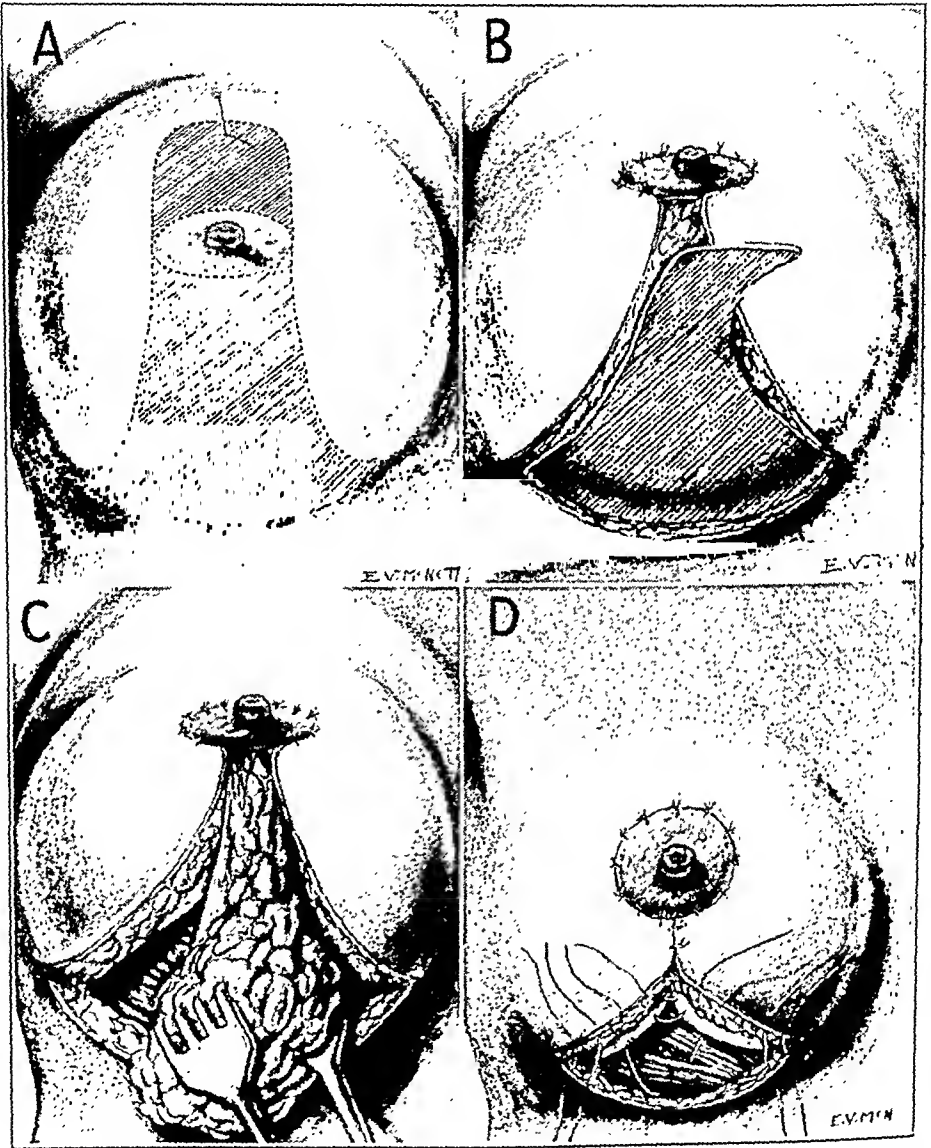
Fig. 1.—*A*, the place to which the nipples are to be transferred is marked with a pin; the areola is circumscribed by an incision and the parts of skin to be resected are outlined. *B*, the skin above the areola is excised; the areola is lifted and sewed into the upper corner of the defect; the skin beneath the areola outlined by the previous incision is partly detached. *C*, the skin beneath the areola is excised; the hypertrophic breast tissue is removed. *D*, the wound is closed in layers; the lower edge of the breast is anchored to a bridge flap of the major pectoral muscle.

Lexer,[3] as far as can be ascertained, was the first to devise this method. His operation, which I am adopting, might be described as follows: After the usual preparation and with the patient under complete anesthesia, the two points to which the nipples are to be transferred are marked with a pin, so that comparison as to normal position and correlation can be made (fig. 1 *A*). The areola of one side is then circumscribed by an incision, and above this is excised a piece of skin of the same width as the areola and with a rounded end as far above the pin as the nipple is distant from the margin of the areola. After this excision, the skin beneath the areola is incised in continuation of the upper cuts, not parallel, but in diverging curves, so that the terminal parts of the incisions lie within the fold of the breast. An incision running along this fold completes the outline of that part of the skin which is to be excised later. The areola is then lifted and sewed into the upper corner of the defect (fig. 1 *B*). The hypertrophic part of the breast now bulges below the areola. The skin beneath the nipple, which was outlined by the previous incision, is next excised. The bulging fatty tissue is now grasped and excised along the edge of the skin and is separated from the pectoral fascia (fig. 1 *C*). After the bleeding is checked, the wound is closed in layers (fig. 1 *D*). The first suture approximates the edges of the wound just below the nipple with a bite through the pectoral fascia. To support the breast from below, a bridge flap of the major pectoral muscle is lifted at the lower edge of the breast. The last suture through the breast tissue is also passed through this flap of muscle. Finally, the skin is closed.

In the case of atrophic breasts, the operation is the same, with the one exception that no breast tissue is excised; the tissue is merely inverted with mattress sutures to erect the breast.

The operation should be done on both sides at one sitting. In most cases, it can be performed in one stage. In cases of unusually large breasts, however, a two stage operation is safer in order not to endanger the nipple.

The cases of 2 patients operated on by me may be mentioned here as examples. The first patient had hypertrophic pendulous breasts of moderate degree (fig. 2). In the second patient the hypertrophy of the breasts was more pronounced (fig. 3). For both patients a one stage operation was employed.

The advantage of this method of plastic operation on the breasts outlined herewith is threefold: 1. Since the planes of the wound curve outward and broaden below, the breast, after approximation of the edges of the wound, becomes erect and pointing rather than flat. 2. The scars,

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3. Lexer, E.: Die gesamte Wiederherstellungschirurgie. Leipzig, Johann Ambrosius Barth, 1931.
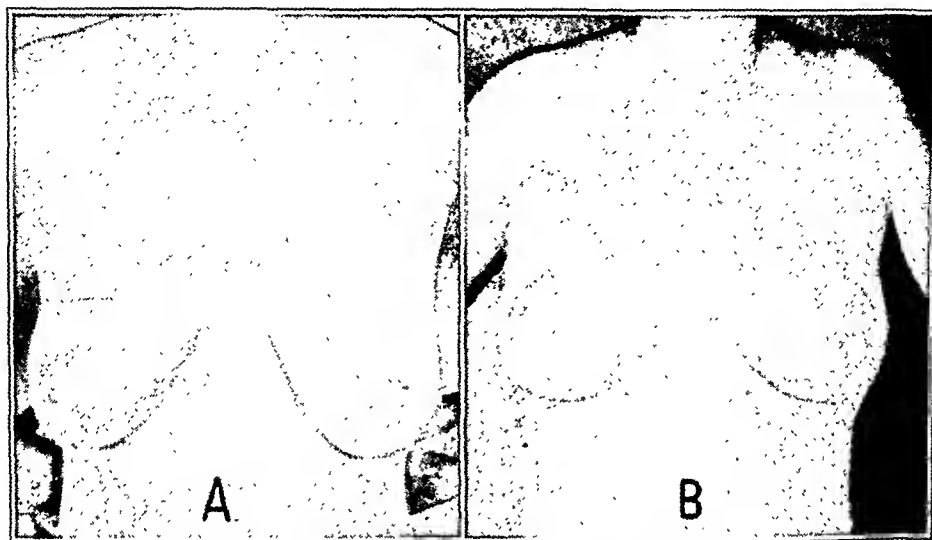
Fig. 2.—*A*, hypertrophic pendulous breasts of moderate form. *B*, same patient five weeks after plastic repair.
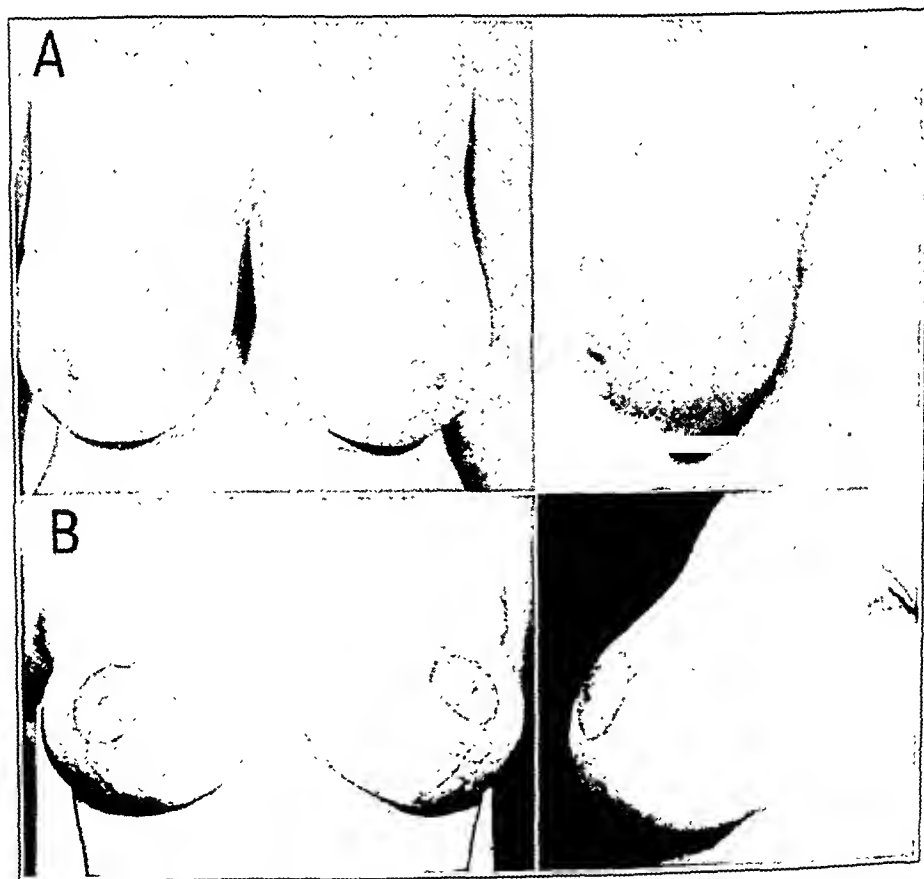

Fig. 3.—*A*, the more pronounced form of hypertrophic pendulous breasts. *B*, the same patient three weeks after plastic operation.

which usually disappear after three months, are situated in the lower half of the breast and in the submammary fold. 3. The function of the gland is not disturbed. On the latter point I have had no experience in my own practice, but I have seen several examples among Lexer's patients.

SUMMARY

Plastic operation on the breasts is more in demand today because of the importance which women attribute to a properly proportioned form. This operation is described in detail, according to Lexer's technic, and two examples are given.

USE OF THE CUTIS GRAFT IN PLASTIC OPERATIONS

ALFRED UIHLEIN JR., M.D.

ROCHESTER, MINN.

A review of the literature on the use of skin in certain types of plastic operations reveals that it has been suggested for application. No reports of conclusive experimental or clinical studies with this easily available autoplastic material have appeared except those articles which have been published in the German literature.

Professor E. Rehn has successfully used this material, which he and Loewe called the cutis graft, in plastic operations. The gratifying results seem worthy of consideration.

To avoid any misunderstanding, it is advisable first to define the term "cutis."

This word was coined by those who suggested the use of this type of skin graft because, though it is derived from the skin, it is not a bona fide skin graft. It does contain the cutaneous and subcutaneous structures of skin, but it is devoid of its epidermal covering when it is transplanted.

The employment of cutis in plastic operations was first advocated by Rehn[1] and Loewe[2] prior to 1914. Rehn, however, first applied it clinically in the treatment of postoperative hernia in cases in which the anatomic structures had been weakened to such an extent by the operation that a plastic repair was required to prevent recurrence. The results in these cases were so encouraging that gradually in the past nine years the field of application has been broadened to include twelve types of surgical conditions in which the cutis transplant was successfully used. In this article some of the experiments which led up to the clinical application of the results will be briefly outlined. This outline will be followed by a description of the operative procedures and by an analysis of the results obtained in the 104 cases in which plastic operations with cutis have been performed in Rehn's clinic since 1928.

Rehn concluded that cutis is the most suitable material for repairing defects because it best answers the requirements for tissue regeneration,

1. Rehn, E.: München. med. Wchnschr. 1:118, 1914. Rehn, E., and Miyauchi: Arch. f. klin. Chir. 105:1, 1914.

2. Loewe, O.: München. med. Wchnschr. 24:1320, 1913.

as outlined by Roux[3] in 1912. Cutis contains all the components of the skin except the epidermis; it is elastic; it is inherently active; and it is composed of a rich network of connective tissue fibers. After its transplantation these inherent factors assist in the metamorphosis of the graft. Owing to the stimulus set up by the tension under which the graft has been sewn, a gradual metaplasia of the transplant takes place. The inherent activity of the graft accelerates repair by encourging immigration of the cellular elements. Fascia, since it is inactive, acts only as a conductor of the migrating cellular elements, Rehn stated. Because of its histologic structure it can permit regeneration only in two planes at right angles to one another.

Rehn[4] and Schwartz[5] in experiments on dogs performed a tenotomy of the achilles tendon and closed the defect with a cutis graft. Under the influence of the functional *Reiz* elicited by their procedure of fixation of the graft to the tendon stumps, a gradual metamorphosis of the cutis into a tendon difficult to differentiate from a normal tendon occurred in about ten weeks. Transplanted fascia regenerated more slowly and failed to repair as well. The explanation lies in the inherent activity and longevity of cutis.

Eitel[6] showed rather conclusively that cutis lives longer and is more active than fascia and therefore is more suitable for plastic repair. He removed pieces of human fascia and cutis at operation and performed metabolic studies on them with the Warburg technic. In the accompanying chart (fig. 1) will be found his evidence of the superior viability of cutis as compared with fascia. Eitel stated that it holds for all age groups.

Schneider[7] found that cutis, like the other tissues which tend to regenerate most satisfactorily, contains no reduced glutathione. He selected reduced glutathione to exemplify a product of tissue oxidation and reduction. He analyzed the reduced glutathione content of various tissues to determine the role played by this substance in the ability of tissue transplants to grow. He found also that tissues which do contain this reduced substance regenerated poorly when transplanted, according to the amount found in them (table 1).

Histologic proof of the activity and the resulting metamorphosis of the cutis transplant was afforded me by the unexpected return of 2 patients on whom cutis operations had been done four years previously.

3. Roux, W.: Terminologie der Entwicklungsmechanik der Tiere und Pflanzen, Leipzig, Wilhelm Engelmann, 1913.

4. Rehn, E., (*a*) in Lexer, E.: Die freien Transplantationen, Stuttgart. Ferdinand Enke, 1924, pt. 2, p. 503; (*b*) cited by Benninghoff: Verhandl. d. anat. Gesellsch. **40**:95, 1931; (*c*) Arch. f. klin. Chir. **186**:244, 1936.

5. Schwartz, E.: Deutsche Ztschr. f. Chir. **173**:301, 1922.

6. Eitel, H.: Deutsche Ztschr. f. Chir. **242**:806, 1934.

7. Schneider, E.: Arch. f. klin. Chir. **186**:267, 1936.

Pieces of tissue were removed from the healed cutis transplant area. Histologically the preparations presented normal connective tissue with its fibrous and fatty components containing their own blood and nerve supply. The abundant vascularity of the tissues was striking. No epidermal remnant of the original cutis graft and no dermoid cysts could be identified. Occasionally large cells with rather large nuclei, deep staining (with hematoxylin and eosin) and lying in rows or in rings were found (fig. 2).

These large cells might be interpreted as remnants of the hair follicles or the sweat glands of the original cutis graft or as macrophages produced by suture material reaction. Cameron,[7a] of Edinburgh, who
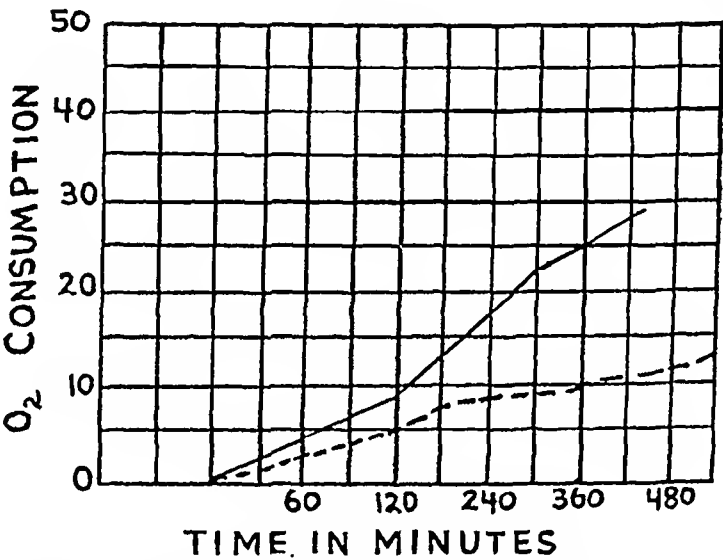
Fig. 1.—Superior viability of cutis as compared with fascia. The solid line represents cutis; the broken line, fascia.

TABLE 1.—*Relation of Gluthathione Content to Transplant Take (Schneider)*

	Reduced Glutathione Content	Outlook for Free Transplantation
Liver	+++	......
Kidney	++	......
Adrenal	++	......
Thymus	++	......
Muscle	++	......
Heart	++	......
Thyroid	+	Only temporary
Testis	+	Only temporary
Blood	......	Only temporary
Bone	......	+++
Fascia	......	+++
Cutis	......	+++
Tendon	......	+++
Fat	......	+++

7a. Personal communication to the author.

has been doing some experimental skin transplantations with guinea pigs, found similar histologic changes postoperatively but was unable to explain their cause. Besides these large cells, round cell infiltration with interspersed giant cells in a rather compact and well defined network of fibrillary connective tissue was found. No scar tissue was seen.

Fig. 2.—*A*, microscopic cross section of tissue excised from an area of previous cutis graft, showing large cells with deep-staining nuclei. *B*, microscopic cross section of the same tissue, showing its rich vascularity and viable connective tissue. No scar tissue is found.

Rehn applied the principles derived from his experimental findings to the plastic repair of human tissues. His first operations comprised the repair of large postoperative abdominal hernias with relaxed skin

and subcutaneous structures, the repair of which by any other form of operative procedure was not assured. Since 1928, 65 patients with hernia have been operated on by him or his assistants, with encouraging results. Sixteen patients failed to reply to a questionnaire sent them and to appear for reexamination. Of the remaining 49, 6 presented recurrences from two to nine years after operation. A ventral hernia before operation and abdominal and thigh wounds after the cutis repair are shown in figure 3. This patient had no recurrence of the hernia
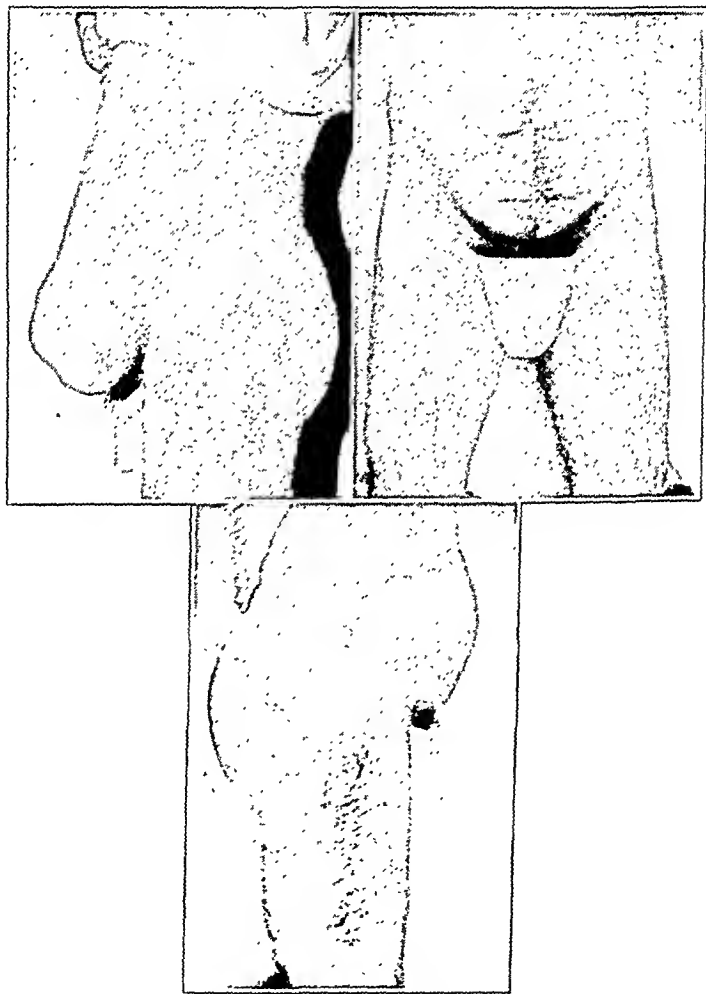
Fig. 3.—*A*, preoperative lateral view of a large postoperative ventral hernia. *B*, anterior view of the patient eight weeks after a cutis graft operation, showing the well healed abdominal scar. *C*, lateral view of the patient, showing good abdominal support and a well healed scar on the thigh at the site from which the graft was removed.

seven years after the cutis plastic repair, despite the relaxed condition of all the abdominal muscular structures before operation.

Gradually the cutis transplant became the tissue of choice for other plastic operations, and to date Rehn has used it successfully in the thirteen different types of cases listed in table 2.

Before discussing the results obtained in the various types of cases in which cutis plastic procedures were employed, the manner in which the cutis is obtained and the prerequisites of a good result will be described. The transplant is usually taken from the lateral side of the thigh. This area, as well as the operative field, is thoroughly cleansed with compresses soaked in 70 per cent alcohol. These are applied daily five to eight days before operation for ward patients and one to four days before operation for private patients. A dressing soaked in a 3 per cent concentration of solution of formaldehyde U. S. P. in alcohol is generally substituted daily for ten minutes to insure better cleansing of the skin. On the day of operation both areas are washed for ten minutes with soap and water and then sponged off with 75 per cent alcohol and draped. No iodine should be used in preparing the area from which the graft is to

TABLE 2.—*Summary of Cutis Operations with Their Results*

Condition	Number	Results Good	Results Poor	Results Unknown
Postoperative hernia	65	43	6	16
Ventral hernia	4	3	..	1
Inguinal hernia	11	8	3	..
Knee joints with lateral motion	8	6	2	..
Habitual dislocation of jaw	1	1	..	..
Chronic dislocation of finger	1	1	..	..
Muscle hernia	2	1	1	..
Ruptured biceps tendon	3	2	..	1
Chronic laceration of extensor tendon	3	2	..	1
Habitual patellar luxation	3	2	1	..
Arthroplasty (elbow joint)	1	1 (for 3 yr.)	..	..
Fascia lata rupture	1	..	1	..
Mammary hypertrophy	1	..	..	1
Total	104	70	14	20

be taken. The desired piece of cutis is not excised until the major portion of the operation has been completed and the muscle groups clearly exposed for good fixation. For obtaining the graft the epidermis is first removed as completely as possible by the Thiersch method. This gives a fresh bleeding surface and minimizes infection. From the area free of epidermis an oval piece of cutis similar in size to the area to be covered or supported is excised to include about 1 cm. of fatty tissue (fig. 4).

The graft is placed in warm saline solution as the edges of the thigh wound are approximated with a running silk suture. After it has been made certain that hemostasis is complete in the area to which the graft is to be sewn, the cutis is placed over the defect. It is then sutured under tension at its upper and lower poles with chromic catgut to the generously exposed muscles and fascia (fig. 5). The graft is next stitched in its entire circumference to the surrounding exposed healthy tissues. It is stretched as much as possible after all the sutures have been securely fixed so that it resembles a taut drumhead. The skin and

subcutaneous tissues of the wound are then easily approximated over the graft, and the wound is closed in the usual manner.

These are the procedures usually carried out in Rehn's clinic for obtaining the transplant and suturing it to the area requiring repair.
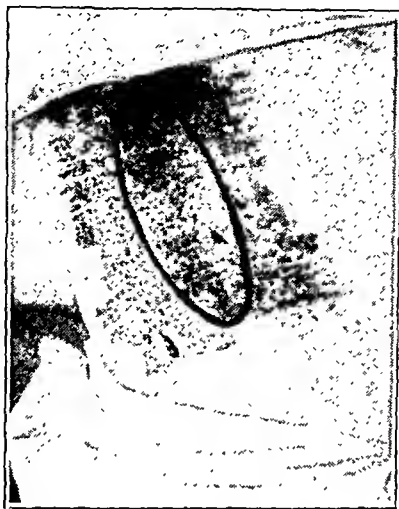

Fig. 4.—Area of the thigh, free of epidermis, from which an oval piece of cutis of the desired dimensions may be excised.
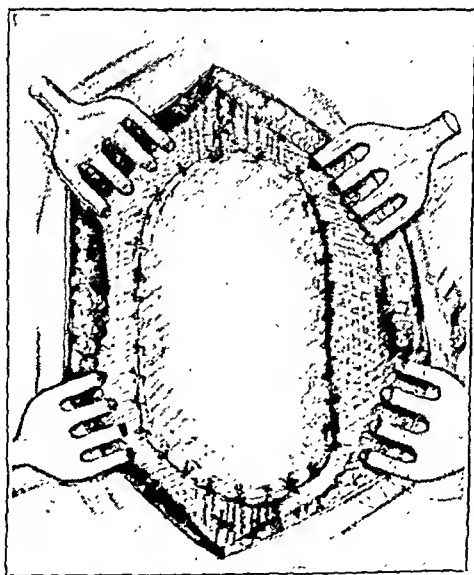

Fig. 5.—Schematic representation of the cutis graft after it has been fixed under tension to the exposed healthy tissues.

For cases in which an abdominal hernia is present and a cutis repair is necessary Rehn developed another operation, known as the "double-breasted vest" or "Türflügel" operation. In this procedure a flap is fashioned from the skin of the abdominal wall and is used as the cutis

graft (fig. 6). This type of operation has its limitations, since inelastic subcutaneous tissues and scarred skin are contraindications to its use. When the patient presents indications for this operation, one half of the incised skin area *abde* (fig. 6 *A*) is used as the cutis flap. After the epidermis has been removed, this flap is excised along the hypothetic line *ad* and is then fixed under good tension over the first stage hernia repair (fig 6 *C*). The opposite skin flap now closes the wound. Rehn has performed only 6 operations of this type in selected cases, with good results in 4 of them. Either of the aforementioned procedures is suitable for the repair of abdominal hernia, but the success of all plastic opera-
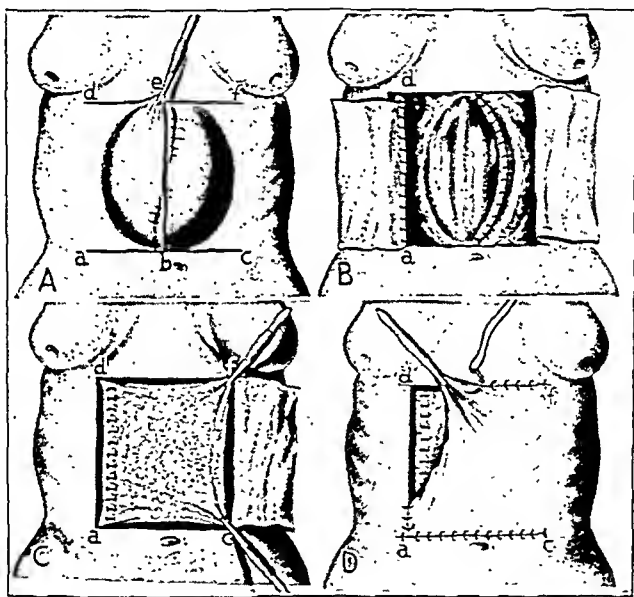
Fig. 6.—*A*, line of incision forming the two flaps used in the "double-breasted vest" operation for repair of ventral hernia. B, cutis flap fashioned from the flap *abde* and fixed with the first row of sutures. C, manner in which the cutis graft is sewn, under tension, over the repaired hernial sac. *D*, final closure of the wound. The anterior flap of skin is sutured over the buried cutis graft. (After Rehn.)

tions with cutis lies in the amount of tension under which the cutis is sewn over the defect. Without this tension the graft does not take satisfactorily.

The tension and pressure evoke the functional stimulus necessary to produce the metaplasia and metamorphosis. Likewise, in such repairs it is essential that a careful dissection with exposure of the muscles and fascia be made, so that accurate and supportive sutures can be placed to maintain the necessary degree of tension.

As was remarked earlier in this article, the cutis operation grew [...] because the procedure of choice for other conditions requiring plastic repair. Some of these, together with their clinical results, will now be surveyed. Beside the patients now having repair of postoperative or ventral hernia, patients with recurrent inguinal hernia, knee joints with excessive lateral motion, rupture of the biceps, tendons, conditions of the finger tendons requiring plastic operations and other conditions (table 2) have been treated with the cutis transplant.

The repair of recurrent inguinal hernia by this procedure was done in 11 cases. Three patients showed recurrence of the hernia after the cutis repair, but the others have remained cured to date, the periods ranging from two to six years. Frank[8] in a recent paper reviewed these cases. From the sketches made at the operation, he found that in the repair of such a hernia a sufficiently large graft must be taken to assure good attachment to the surrounding structures. These attachments are primarily to the symphysis pubis below and to the internal abdominal muscles above, since recurrences usually develop at these points.

The plastic repair of a knee joint with excessive lateral motion by a cutis transplant has been an interesting step in the treatment of this disabling ailment. The cutis graft in such a case is a functional equivalent of the weakened ligamentous supports and aids in checking the lateral motion. Prior to 1933 Rehn made an S-shaped incision along the lateral or medial aspect of the knee, depending on the side on which weakness was present. With the knee slightly flexed, he exposed the lateral or medial muscle groups above the knee and the ligaments around the knee joint. Then he fastened the upper pole of the cutis graft to these. The lower pole he sewed under tension to the previously exposed tuberosity of the tibia below. At present, however, he makes one incision above and one below the knee joint, as illustrated in figure 7.

After freeing the adipose tissue from the outer ligamentous structures of the knee by means of blunt dissection, he sews the cutis to the muscles exposed by the upper incision. Through the incision below the knee he then inserts forceps, drawing the cutis flap down and fixing it under tension to the gastrocnemius muscle. Fixation sutures are then placed at all available points to assure firm attachment of the graft. Rehn no longer attaches the cutis to the tuberosity of the tibia, since the muscular attachment affords more equalized tension than the bony one. In 1 case reported by Brandis[9] the excess lateral motion was marked in both directions, and a bilateral plastic repair was performed, which has given an excellent functional result to date. The patient can again

8. Frank, R.: Grenzen der Bassini Operation und Indikationen zur Kutis Plastik, to be published.

9. von Brandis, H. J.: Zentralbl. f. Chir. 60:130, 1933.

pursue all sports without hindrance. Eight patients with excessive lateral motion of the knee joint have been operated on in the clinic in this manner, with good results in 6 instances. Of the remaining 2 patients, 1 had a slight patellar snap on full extension of the knee but not lateral motion on extension; the condition of the other has remained unimproved. In the cases in which no improvement occurred, it was found that the muscles were not able to maintain the tension under which the cutis was attached, since they had become weakened by the long-standing condition which had allowed lateral motion. When this condition exists, the possibilities of a good result are slight. In all these cases some degree of lateral movement could be induced when the knee was flexed but not when it was extended. Results in the other cases in which operation and repair with the cutis technic were performed are given in table 2.
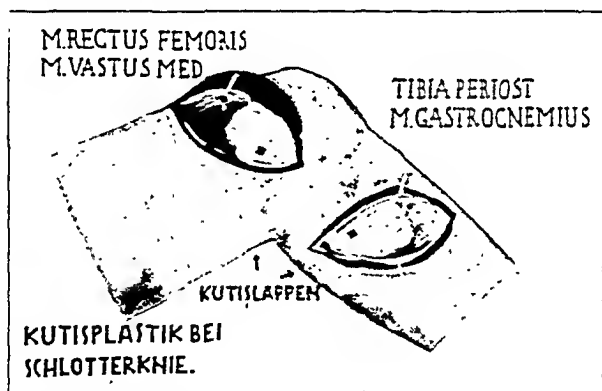
Fig. 7.—Sketch of the approximate position of the cutis graft with relation to the muscle groups and surrounding structures in the repair of knee joints with excessive lateral motion.

Two of these cases are of particular interest. In the first, a cutis transplant was used in the operative treatment of habitual dislocation of the jaw, and in the second the graft was used in conjunction with an arthroplasty which was performed because of an ankylosed elbow joint (fig. 8). The latter case was reported by Rehn.[10] The arthroplasty gave a good result without any limitation of motion until three years after operation, when the patient fell and fractured an epicondyle. Since that time the patient has been unable to extend the forearm fully. The other patient has had no recurrence of the dislocation.

Associated with any operative procedure are complications which may arise unexpectedly. Complications do occur after cutis plastic operations, but the majority of them do not necessarily cause a poor result.

10. Rehn, E.: Zentralbl. f. Chir. **61**:1563, 1934.

Good anesthesia constitutes the good result. The anesthesia must be sufficiently deep to secure complete relaxation of the muscles, so that the necessary degree of tension is sustained. Without sufficient relaxation, the cutis, which appeared tense at operation, will become relaxed and recurrence will be imminent. Spinal anesthesia and intravenous anesthesia have been tried, but ether anesthesia has given the best results.

Wound infection and hematoma formation comprise the principal early complications, but are not so common as one might expect. Fifteen of 101 patients had wound infection, and 5 had hematoma, complicating the postoperative course (Table 3). In 9 of the first group,
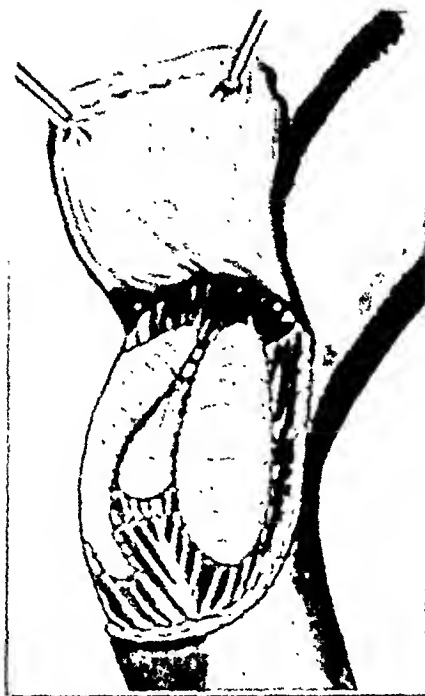
Fig. 8.—Half-schematic representation of the cutis graft in an elbow arthroplasty, as the functional equivalent of the ligaments.

there was good healing in spite of the infection, and no recurrence of the preoperative symptoms was observed. Two patients failed to appear for examination. Of the remaining 4 patients, 3 had erysipelas of the wound and the fourth a streptococcic infection. Neither of these was benefited by the operation. A severe wound infection caused by virulent aerobic or anaerobic organisms precludes a good result. Nonspecific infections cause little uneasiness, since the graft is active and metaplasia will proceed despite the infective process. Of those patients in whom a hematoma developed (the hematomas were usually caused by insufficient hemostasis of the bed of the wound), all but 1 had a normal postoperative course after the aspiration of the hematoma.

These figures show conclusively that complications by infection tended to hinder in only a slight degree the regenerative potentialities of the transplant and that antipathy to skin as a potential source of infection is probably unfounded. Fat necrosis with secretion, which often accompanies the simple infective process, requires local compress treatment for a few days, after which the wound heals per primam intentionem. The area of the thigh from which the cutis was taken healed somewhat slowly, but in all cases after six months' time the scar was scarcely visible.

The question of length of hospitalization or of the influence of the age of the patient on recovery may arise. All patients were kept in bed from four to ten weeks to assure good healing. Of all the cases, including cases of both ward and private patients, the average duration of hospitalization was from six to ten weeks for the former and from four to six weeks for the latter. The average age of all the patients was 51 years. The youngest patient was 5 years old, and the oldest was 85.

TABLE 3.—*Complications Following Plastic Operations with Cutis*

Complications	Number	Good Results	Poor Results	Results Unknown
Wound infection	15	9	4	2
Hematoma	5	4	1	..
Death from pneumonia	4	..	..	..

Both of these showed good postoperative results four years after operation. This would indicate that the patient's age has no important influence on the result of plastic operation with cutis.

SUMMARY

In this article a type of plastic operation performed at the clinic of Prof. E. Rehn in Freiburg, Germany, is described. The cases of the 104 patients operated on by this procedure since 1928 have been analyzed in the hope that the recorded results may stimulate the further use of the cutis transplant. Cutis is better suited for plastic repair than fascia, for it is active and has a longer life than the latter. Cutis is more easily available, since the graft can be taken from any area of the body; the source of fascia, on the other hand, is limited. In adipose persons, fascia is generally friable and thin and can be excised only in strips, but with cutis no such limitations exist. The removal of fascia incurs the risk of a postoperative muscle hernia. No herniation of the area from which the cutis was excised occurred in the cases just reviewed. Furthermore, cutis encourages tissue regeneration by the functional stimulus evoked by the tension under which the graft had been sewn. Generally metaplasia progresses despite wound infection. The operative procedure is not

difficult. If the same time ... are carefully prepared ... and anesthetic administered ... and the ... as described, the patient will ... an ... postoperative result

CONSIDERATIONS

In any plastic operation in which ... is used the following essential principles must be observed:

1. The skin in the operative area must be given careful preoperative preparation.

2. All necessary ... reconstructive ... must first be attended to, such as the Bassini repair of an inguinal hernia or a Mayo-Pfannenstiel reconstruction of an abdominal hernia, before the cutis graft is sewn in place.

3. The muscle and fascia groups to which the cutis is to be attached should be anatomically dissected out and brought into view to facilitate good fixation of the graft.

4. All bleeding vessels in the wound bed must be ligated prior to transplantation to prevent formation of a postoperative hematoma.

5. It is all important that the cutis graft be sewn to the surrounding tissues under the greatest possible tension.

MESENTERIC LYMPHADENITIS

REPORT OF TWENTY-FOUR CASES WITH TABULATIONS SHOWING RELA-
TION TO APPENDICITIS AND OTHER DISEASES; NEED OF BETTER
UNDERSTANDING OF THE MESENTERIC LYMPH NODES

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A continuation of the review of the hospital charts from Aug. 1,
1936 to Sept. 1, 1937 on which has been noted a definite record of
diseases of the mesenteric lymph nodes shows more than was reported
in the detailed analysis covering 123 cases observed during the years
from 1914 to Aug. 1, 1936, previously published.[1] Proportionately, as
has been pointed out, more attention is being paid to the lymphatic
system generally and particularly to the lymph nodes within the abdomen
than was given to these structures ten or twenty years ago. It was
much longer ago than this, however, that tuberculosis was believed to be
the cause of most lesions of the mesenteric nodes; attention was given
to nonspecific mesenteric lymphadenitis only about 1920 and thereafter.

Numerous articles have appeared since 1900 reporting the asso-
ciation of the symptoms of mesenteric lymphadenitis with those of infec-
tion in the vermiform appendix. Some authors have said that mesenteric
lymphadenitis is indistinguishable from certain types of appendical dis-
ease, and others have gone so far as to say that mesenteric lymphadenitis
can be readily differentiated from appendicitis before operation or even
without operation. I hesitate to agree with the latter.

It is high time that a more definite understanding be reached between
practicing physicians and investigators of the disease syndrome called
mesenteric lymphadenitis. From the observation of 123 case histories
previously studied and of 24 additional cases for comparison, I believe
that certain definite statements on the various characteristics of the dis-
ease can be given out.

For detailed development of the hypothesis that stasis in the gastro-
intestinal tract, chronic disease of the liver, constipation and many other
conditions may predispose to the development of infection of the mesen-
teric lymph nodes the original article must be referred to.[1]   That

appendicitis of different types may be associated with involvement of the mesenteric nodes is indicated by the observations in the 123 cases previously reported and also by the profuse literature on the subject, which is probably not sufficiently appreciated.

It cannot be denied that there is a discrepancy between the clinical descriptions of mesenteric lymphadenitis given by some investigators and the findings of the majority of surgeons operating in the abdomen. The reason for this is that many have neglected to notice the condition of the mesenteric lymph nodes at the time of operation. There is a great difference in clinical opinion as to the normal limits in size of the lymph nodes and the anatomic characteristics of disease in the deeply buried lymphatic structures of the mesentery. Careful thinking on the subject, however, does not permit an escape from certain definite opinions on the questions of diagnosis and treatment.

Further proof than that a patient with infection of the cervical lymph nodes had an original portal of entry of the offending germ somewhere in the mouth or the upper part of the respiratory tract is seldom given any serious consideration unless the point of entrance is still causing trouble or is believed to be continuing the pathologic process in the lymph nodes of the neck. Infected teeth, tonsils and sinuses are all old subjects now, a little out of style and somewhat hackneyed as a topic for discussion. In spite of this the surgeon must maintain an interest in the cause of infection of the glands of the neck, and he does this by insisting on good cooperation from the otolaryngologist. The surgeon, then, recommends that the teeth and upper respiratory tracts of all patients be studied for the point of origin of the infection. Often there is little to account for the cervical infection, which is seldom diagnosed from a truly scientific point of view.

So it is with the operative finding of infection of the mesenteric lymph nodes. As a rule the operator takes out a mildly diseased appendix, hoping that a diagnosis of chronic appendicitis will satisfy the patient and that appendectomy will produce good results. The feeling that there is some other cause than "just a chronic appendix" has stimulated discussion as to what does cause the atypical abdominal symptoms which sometimes occur and are not relieved by a simple appendectomy. No one seems to have answered this question conclusively.

It is only natural that the majority of practitioners must become confused by such a state of affairs. The opinion of the most careful of clinical investigators on the subject of intra-abdominal disease should be emphasized more frequently than it is: namely that every case should be studied individually, so as not to receive a much abused general diagnosis or one based on few physical signs and no truly scientific principles.

There is good evidence that chronic appendicitis should be discarded as a blanket diagnosis covering all the indefinite pathologic conditions which frequently lead to celiotomy. There is good evidence, furthermore, that the mesenteric lymph nodes and the large plexus of lymphatics in the mesentery have been underestimated, to say the least, as to their function and import in physical diagnosis.

If the analogy of infection of the cervical lymph nodes may again be alluded to, it would be wise to remember that tonsillitis with its attendant involvement of the lymph nodes is seldom given the additional diagnosis of cervical lymphadenitis. So, likewise, at the time of celiotomy, few surgeons have bothered to note the presence of mesenteric lymphatic infection until comparatively recently, unless no other diagnosis for the intra-abdominal symptom could be reached. None the less, however, they probably have been persistently correct in removing the appendix, for of course numerous patients have remained well and have never been seen again. If little emphasis was ever put by these surgeons on the mesenteric lymph nodes, there can be little hope of proving that the nodes were ever involved, providing the patients have generally remained as well as they have appeared to do.

On the basis that infection in the mesenteric lymph nodes is comparatively common but is insufficiently appreciated as being able to give rise to symptoms either alone or in conjunction with many other conditions, I should like to emphasize to all physicians who diagnose intra-abdominal disease that infection of the mesenteric lymph nodes is a real entity and is not to be forgotten at any time.

When it is diagnosed or suspected it cannot be safely dropped from consideration, or "shelved." It should mean that the physician has accounted for some of the symptoms. In addition, his discovery that the lymph nodes are affected should indicate to him that an extensive and important group of structures must be included in his consideration of the possible cause of the condition, the treatment and the prognosis. A great step will have been taken when surgeons have learned that the mesenteric lymph nodes are as important in relation to the rest of the gastrointestinal tract and to the appendix as are the cervical nodes to the upper respiratory tract and, for example, the teeth. One must not forget, moreover, the importance of the remainder of the lymphatic structures in the body, especially the largest groups of all, the mesenteric and retroperitoneal groups.

Any proof that the surface lymph nodes of the body are all involved in any pathologic changes, either acute or chronic, should point to the likelihood, if not the certainty, of similar changes in the intra-abdominal lymph nodes. A moment's recollection of the close anatomic connection between the branches of the splanchnic nerves, the

nerve plexuses, the branches of the mesenteric vessels and the mesenteric lymph nodes—which are contiguous—must be of value to the physician who wishes to arrive at any conclusion about vague disease symptoms in the abdomen. The innumerable pathways of the mesenteric plexus and the symptoms that might arise from the countless irritations of the vasomotor nerves in the walls of the mesenteric vessels which may have been stimulated by infection of the mesenteric lymph nodes offer endless considerations as to refinement of diagnosis, but unfortunately little that is uniform and consistent enough to teach as a real symptom complex.

Because of the fact that some investigators have been very definite about the ease with which mesenteric lymphadenitis can be diagnosed, I feel that this teaching should be discontinued. My statement that the condition is not always easy to diagnose is given weight by the numerous authors who have frankly admitted the difficulty of ruling out atypical appendicitis and have been mentioned earlier.[1]

The frank interpretation of cases studied at the New York Post-Graduate Hospital over a long period of years seems to bear out this statement.[1]

From the first study and also from the cases observed from Aug. 1, 1936 to Sept. 1, 1937 in the same hospital, it is apparent that when the mesenteric lymph nodes are noted at operation to be diseased, there may have been many and varied symptoms; the condition may have been acute, or it may have been subacute or chronic, with abdominal distress dating back many years. There are cases of intra-abdominal malignant neoplasm with infection in the mesenteric nodes that could not possibly be diagnosed preoperatively by any of the syndromes which have been attributed to either acute or chronic mesenteric lymphadenitis.

Each patient must receive a careful physical examination, including especially a search for foci of infection in the upper part of the respiratory tract, the gallbladder, the colon, the rectum and the appendix. Ova and parasites must be ruled out. Stasis in the gastrointestinal tract, recurrent abdominal symptoms of even mild digestive distress, spasm of the rectal sphincter and constipation must all be recorded if the cause of the disease of the lymph nodes is to be understood and properly treated.

In the cases of mesenteric lymphadenitis it is most important to note that there may be no abdominal signs whatever, or there may be only a tenderness to the right of the umbilicus at McBurney's point or a little above it. Spasm and rigidity are less common, and when they occur they do not help much either to rule out the diagnosis or to establish it. Some physicians apparently do not note the special signs, such as the shifting dulness when the patient turns on either side, or the shift in the tender-

ness to the left of the umbilicus when he turns on the left side.   Such physical signs as either of these are open to considerable misinterpretation, although they should not be forgotten.

The diagnosis is not regularly made preoperatively, nor is the condition found alone except in extremely rare cases.   In this hospital the positive proof of an infection in the appendix at some time has been found in almost 90 per cent of all operative cases of mesenteric adenitis.

The treatment is most important and requires particular emphasis. The patients for whom nothing but simple appendectomy was performed showed an entirely different mortality and morbidity average from that observed among patients on whom a more extensive operation was performed.   The comparison, of course, is similar to a comparison of a number of different diseases, any and each one of which may carry its own higher rate in complete independence of the "incidental" mesenteric lymphadenitis.   The low rate of occurrence of complications of all kinds when simple appendectomy was done would indicate that the time has come to encourage the removal of the appendix, not only because there is nothing else to remove but also because of this little appreciated disease, mesenteric lymphadenitis.   It especially should be described to the patient and cited as a reason that something is wrong besides "just an appendix."   A complete search for the underlying causes of the disease ought also to be made.

I believe the patients with insufficiently studied mesenteric lymphadenitis, for whom a vague diagnosis is made and who are not given a new hygienic regimen so as to do away with their deep-seated predisposition to infection of the mesenteric lymph nodes (if it is not entirely due to infection or malposition of the appendix) compose the large group who are not relieved by appendectomy and often require a later celiotomy.

I feel that certain organs are sites of predilection for certain organisms and that when a lymph node shows involvement it must indicate that the infection has already gone by some barrier to reach the node. It must mean that the infection is one that elects to infect lymph nodes or one by which the lymph nodes are especially affected.   Further, it must mean that when several nodes are affected there is a strong likelihood that extension to the next group of lymphatics or to the blood stream itself (as in peripheral adenitis and lymphangitis in an extremity) may occur when the mesenteric infection is not well understood and treated.   The work of Braithwaite [2] admirably bears out this belief. Heyd [2] has done much to point out many of the steps taken by disease in the abdomen to affect the liver—often by way of the lymphatics.   He

2. Cited by Foster.[1]

is in complete agreement with Alvarez and Adami on the subject of sub-infection of the gastrointestinal tract as a cause of hepatic disease and of repeated insults to the mesenteric lymphatics.

TABLE 1.—*Age and Sex Incidence*

Age	Number of Cases	Male	Female
Under 1 year	0	0	0
1- 6 (incl. 6)	5	3	2
7-10 (incl. 10)	5	3	2
11-16 (incl. 16)	2	1	1
17-21 (incl. 21)	4	0	4
22-29 (incl. 29)	3	1	2
30-37 (incl. 37)	0	0	0
38-72 (incl. 72)	5	2	3
Total	24	10	14
Under 21	16	7	9
21 and over	8	3	5
16 and under	12	7	5
10 and under	10	6	4

TABLE 2.—*Data in Twenty-Four Cases of Mesenteric Lymphadenitis*

Average age	19.4 yr.
Sex	10 M, 14 F
Died	1, or 4%
Acute appendicitis	2, or 8%
Subacute appendicitis	11, or 46%
Chronic appendicitis	9, or 38%
Appendectomy	21, or 88%
Other operations	9, or 38%
Evidence of upper respiratory tract or marked focal infection	6, or 25%
Evidence of disease in appendix at any time	21, or 88%
Clinical mesenteric tuberculosis	3, or 13%

TABLE 3.—*Further Data in Twenty-Four Cases of Mesenteric Lymphadenitis*

Average age	19.4 yr.
Sex	10 M, 14 F
Chronic mesenteric lymphadenitis	20, or 84%
Acute mesenteric lymphadenitis	3, or 12%
Purulent mesenteric lymphadenitis	0 0
Pronounced clinical mesenteric tuberculosis	3, or 12%
Associated appendical disease at any time	21, or 89%
Associated visceroptosis or constipation	8, or 34%
Fecal material+ or fecalith++ in appendix	11+, or 44% 5++, or 21% 16, or 68%
Associated gallbladder disease at any time (proved)	2, or 8%

It will be interesting to note a few brief summary tables of the findings in cases of mesenteric lymphadenitis observed at the New York Post-Graduate Medical School and Hospital from Aug. 1. 1936 to Sept. 1, 1937, so as to compare them with what was previously found.[1]

The most interesting findings in these tables have to do with what has gone before. The study of the first 123 cases of mesenteric lymphadenitis recorded in this hospital during a period of twenty-two years revealed certain apparent results.[1] There was a chance to check them because the first half of the group were tabulated separately and at different times before data on the second half were added to the statistics.

The fact that as many as 24 additional cases were observed in the year following the recording of the first large series makes the close inspection of these 24 case records especially worth while. This is true particularly because of the almost identical percentages and averages in this small series and in the original, larger groups.[1]

TABLE 4.—*Summary of Clinical Findings*

Average age..	19.4 yr.
Sex.................................	10 M, 14 F
Preoperative vomiting..............	12, or 50%
Distention or tympany............................	2, or 8%
Spasm of abdominal muscles..........	4, or 16%
Abdominal mass..	2, or 8%
Rigidity..	2, or 8%
Tenderness............................	13, or 54%
Recurrent preoperative symptoms.......................	20, or 84%
Average white blood cell count..	9,300
High average preoperative temperature......	100.2 F.
High average preoperative pulse rate..................................	90
High average postoperative temperature...................................	101.9 F.
High average postoperative pulse rate....................................	115
Other abdominal disease..	11, or 46%
Clinical tuberculosis of the mesenteric lymph nodes.............	3, or 12%
Deaths..	1, or 4%

CONCLUSIONS

Mesenteric lymphadenitis is a little understood disease that cannot always be diagnosed alone but must not be considered any the less important because of this fact.

Vague abdominal symptoms not apparently caused by any definite disease of any particular organ should draw the physician's attention to the mesenteric lymph nodes, if only because of the intimate association between the mesenteric nerve plexus, the mesenteric arteries and veins and the mesenteric lymph nodes themselves.

The high incidence of stasis in the gastrointestinal tract both in this series of cases and in the cases of the earlier report [1] seems to offer the best approach to the problem of determining the most healthful regimen for the patient on whom appendectomy is performed for this disease.

The mesenteric lymphatics are not sufficiently emphasized as to their functional importance both in health and in disease. The average layman

knows about the "glands" in the neck, but he and many physicians know little or nothing of the function of the largest group of lymph nodes and lymphatics in the body—the mesenteric and retroperitoneal groups. Medical and lay teaching should include more detailed studies of these structures.

Appendectomy is the treatment for mesenteric lymphadenitis; it should be performed as soon as the diagnosis is made. Indications of other intra-abdominal disease do not furnish any excuse for neglecting the appendix. Other pathologic conditions of the abdomen should likewise indicate the need of surgical intervention in addition to appendectomy, when necessary.

Infection involving lymph nodes in any part of the body (especially in the neck) should remind the examiner of the numbers of mesenteric nodes which may be also infected.

The vermiform appendix becomes more important than ever before because of the high percentage of diseased appendixes observed in a total series of 147 cases of mesenteric lymphadenitis (in all but 2 of which the diagnosis was proved), from the records of the New York Post-Graduate Medical School and Hospital, Columbia University. The last 24 of these cases are tabulated in this paper, and the data closely resemble those in the cases already reported.[1]

SPLENECTOMY IN TREATMENT OF PROVED SUBACUTE BACTERIAL ENDOCARDITIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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A case of proved subacute bacterial endocarditis in which the condition was treated by splenectomy is herewith reported in detail. The patient is alive and well at the time of writing, more than twenty months after splenectomy. I recognize that twenty months is a short time, but the patient is so completely well that when one considers how hopeless the outlook was only a few months before, the case seems worth reporting.

REVIEW OF LITERATURE

In reviewing the literature I discovered that the effort to alter by splenectomy the insidious course of subacute bacterial endocarditis had been made first in the United States by Riesman,[1] then in Europe by Nordmann,[2] then in South America by Escudero and Merlo[3] and finally in Russia by Sawadski.[4] Other sporadic efforts have been reported by the Mayo Clinic,[5] by Heilborn.[6] by Wieden[7] and by Riesman, Kolmer, and Polowe.[8]

A critical analysis of the 15 csaes thus reported shows that in only 3 was the diagnosis proved prior to operation by cultures of the blood.

1. Riesman, D.: Chronic Septic Endocarditis with Splenomegaly: Treatment by Splenectomy, J. A. M. A. **71**:10 (July 6) 1918.

2. Nordmann, A., in discussion on Endocarditis lenta, Verhandl. d. deutsch. Gesellsch. f. Chir. **45**:240, 1921.

3. Escudero, P., and Merlo, E. V.: Splenectomy in the Treatment of Endocarditis, Rev. de la Soc. de med. int. **1**:361, 1925.

4. Sawadski: Russk. klin. **4**:875, 1925.

5. Mayo, W. J.: Surgical Aspects of Diseases of the Lymphoid Organs, with Special Reference to the Spleen, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1929, vol. 21, p. 638.

6. Heilborn, E.: Is It Possible to Influence Ulcerative Endocarditis or Sepsis by Extirpation of the Spleen? Med. Klin. **22**:535, 1926.

7. Wieden, L.: Splenectomy and Re-Examination of Persons Subjected to It: Twenty-Year Follow-Up, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **44**:13, 1935.

8. Riesman, D.; Kolmer, J. A., and Polowe, D.: Splenectomy in the Treatment of Subacute Bacterial Endocarditis, Am. J. M. Sc. **192**:475, 1936.

The patients in all 3 of these cases were dead within fifteen weeks after splenectomy. One died four weeks after the operation, of femoral and pulmonary embolism; 1 died eight weeks after the operation, of cerebral embolism; 1 died fifteen weeks after the operation, also of cerebral embolism.

It appears, then, that the case herein reported is the first proved case of subacute bacterial endocarditis in which the patient recovered after splenectomy.

Of the 12 patients in whose cases the diagnosis was not proved, 6 were dead within three months after splenectomy, 4 died between seven and twelve months after splenectomy and 2 were alive and well at the time the reports were made (1 six months after splenectomy; the other when he left the hospital). Both the proved and the unproved series are too small to be useful in the drawing of safe conclusions. Thus far, one may state with caution that splenectomy may prove to be most beneficial in cases in which subacute bacterial endocarditis is suspected but is unproved. A summary of opinions of the benefits to be derived from splenectomy in the treatment of subacute bacterial endocarditis may be helpful.

1. In a general article on the spleen, W. J. Mayo [5] in 1929, in discussing various types of septic splenomegaly, stated that splenectomy done for the relief of subacute bacterial endocarditis was without benefit to his patients. Giffin [9] has given me data on 2 of Mayo's cases in which splenectomy was done and in which the patients were probably suffering from subacute bacterial endocarditis. Both of these patients died at home, one three months and one seven months after splenectomy; permission for necropsy was not obtained. A single culture of the blood in each case was sterile. The diagnosis was made from the clinical symptoms. Pathologic examination of the spleens showed nothing of diagnostic importance; there was considerable decrease in fibrous tissue.

2. Nordmann [2] stated that a patient with endocarditis lenta was splenectomized by him four months previous to the time of his report and was doing well. A second patient had been operated on a few days previously and also was doing well. (See follow-up on these two cases by Heilborn.) Nordmann stated that his rationale is that splenectomy serves as a stimulus to the remaining endothelial system in the liver, the bone marrow and the lymph glands, thus stimulating erythropoiesis and leukocytosis.

3. Heilborn [6] reported the end results in Nordmann's 2 cases. The patient in the first case returned to work eight weeks after splenectomy, feeling entirely well. Six months after splenectomy he died of cerebral embolus. Prior to splenectomy this patient had all the symptoms of

9. Giffin, H. Z.: Personal communication to the author.

endocarditis lenta. Five days before admission he had noticed a sudden, severe pain in the left side of the hypochondrium. When removed the spleen exhibited several recent infarcts. It was enlarged, but no bacteria were found.

The second patient had complained of dyspnea and sweats associated with elevation of temperature in the evening. The diagnosis was endocarditis. Several cultures of the blood were sterile. This patient improved after the removal of a large splenic tumor. Cultures of the blood made postoperatively showed a few colonies of diplococci. Three weeks after operation the patient became much worse. Symptoms of aneurysm developed, and a few months later he died of a ruptured aneurysm with terrific hemoptysis. This patient had had syphilis a few years before; he had been heavily treated with antisyphilitic therapy, and his Wassermann reaction on admission to the hospital was negative.

Heilborn concluded that the improvement following splenectomy in cases of endocarditis lenta can be explained only through the elimination of one of the chief foci of infection. He stated that splenectomy performed early in the course of the disease should give good results. One of the indications for splenectomy in this condition is severe pain in the splenic area.

4. Escudero and Merlo [3] reported a proved case of subacute bacterial endocarditis; there was a history of syphilis. While the hypochondriac pains disappeared after splenectomy, the general condition remained unchanged. The patient died a month or so later of pulmonary embolism. The spleen was enlarged; it contained multiple infarcts and exhibited slight perisplenitis. These authors expressed the opinion that splenectomy was not justifiable in this condition.

5. Sawadski [4] reported a case of subacute bacterial endocarditis in which the condition was treated by splenectomy. The patient was alive and well at the time of the report, six months later. The diagnosis was not proved, but Sawadski stated that bacteremia is not a contraindication to splenectomy. He concluded that the spleen in this condition acts as a focus of infection.

6. Wieden [5] reported 5 cases. In 1 case, in which the patient did well but could not be traced, the diagnosis of endocarditis was doubtful. In no instance were cultures of the blood reported, if they were done. In 3 cases the diagnoses were obtained at postmortem examination, one diagnosis being endocarditis lenta, the second being lymphatic leukemia and endocarditis and the third being recurrent vegetative endocarditis. In a fifth case, in which the patient died two months after the splenectomy the diagnosis could not be confirmed, as no autopsy was done. In spite of the poor results obtained, Wieden felt that splenectomy is justified because with the spleen is removed, in some cases, the main focus of infection.

7. Riesman, Kolmer, and Polowe,[5] in summarizing their conclusions based on 4 cases plus a review of the 11 cases previously mentioned, stated :

Splenectomy may prove to be a method of dealing with intractable forms of sepsis without discoverable focus in which splenomegaly is a prominent feature. This group, in which subacute bacterial endocarditis may be suspected but is unproved, at present promises the best results from the operation.

8. My own opinion is based on 2 proved cases, case 2 reported in the tripartite paper aforementioned [8] and the case herein reported. I believe that when subacute bacterial endocarditis manifests progressive secondary anemia associated with splenomegaly and pain in the left side of the hypochondrium, splenectomy is of definite palliative value. Such splenectomy seems to act as a substitute for transfusions by arresting the progress of the anemia and producing ultimate improvement in the hemoglobin and erythrocyte content of the blood. The white blood cell content is increased, and in cases in which the condition is associated with thrombocytopenia the platelet count is lifted to normal levels. Abdominal and articular pains have disappeared after splenectomy, and a quieting effect on the action of the heart has been noted. I believe that the spleen is a continuous source of reinfection and of absorption of bacterial toxins. In both cases the patients' chief complaint, abdominal pain, was entirely relieved. The first patient died fifteen weeks later of cerebral embolus. The second patient is alive and well more than twenty months later. A detailed report of the successful case follows.

REPORT OF CASE

A white girl aged 12 complained of weakness, anorexia and pain in the left upper quadrant of the abdomen, of two months' duration. The family history was noncontributory. The patient's tonsils and adenoids had been removed in 1930. She had had an attack of acute pyelitis in 1931. Her health had been otherwise satisfactory.

About the middle of March 1937 the patient was taken to one of the hospital clinics. No diagnosis was made, but she was ordered to report back to the clinic for patients with cardiac disease. The parents then put the patient to bed, and I was called in to see her on the night of March 17.

Physical Examination.—The temperature was 105 F. and the pulse rate 90; the pulse was regular. The respiratory rate was 20, and the respirations were normal. The blood pressure was 108 mm. of mercury systolic, and 64 mm. diastolic. The weight was 69 pounds (31.4 Kg.). There was some evidence of wasting, and the patient had a pale, wan look.

The lower molars on both sides were decayed. The tongue was coated. There was one petechial hemorrhage in each conjunctival sac.

The glands in the cervical, axillary and inguinal regions were easily palpable.

The lungs were normal. The heart disclosed a mitral systolic murmur, which was transmitted a short distance into the axilla. The heart was enlarged, the point of maximal impulse being almost at the nipple line (see illustration).

The abdomen was soft. Tenderness over the splenic area was easily elicited. The spleen was enlarged so that the lower pole of it rolled over the examining fingers. The liver was enlarged downward almost to the level of the umbilicus.

Vaginal and rectal examinations were not done, except to inspect the introitus for the possible presence of vaginitis. There was no evidence of vaginal discharge; the mucosa looked clean and healthy.

There was one ecchymotic area on each tibial surface in the upper third of its length.

Roentgenogram of the chest. There is no evidence of pulmonary infiltration. The cardiac shadow is enlarged, with obliteration of the pulmonic curve, which is indicative of a lesion of the mitral valve.

The deep and superficial reflexes were intact.

Laboratory Findings.—The results of examination of the blood are presented in table 2.

A culture of the blood was made March 18. The report, one week later, was "no growth." A second culture was made April 7. The report, several weeks after splenectomy, was "pure culture of streptococci obtained in anaerobic medium." This could not be further identified on the ordinary subculturing mediums. It should be noted that splenectomy was performed before positive knowledge of the underlying disease was obtained.

Biopsy of material from the right axillary lymph gland, removed March 25, was reported on by Dr. Hans Wassing, pathologist, as follows: "Nonspecific hyperplastic and chronic inflammatory (?) changes."

TABLE 1.—*Summaries of Proved and Unproved Cases of Subacute Bacterial Endocarditis in Which Splenectomy Was Done*

No.	Date Reported	Where Done	Age	Bacteria in Cultures of Blood?	Final Results and Comment
		Group 1: Proved Cases in Which Splenectomy Was Done			
1	1925	Argentina...............	28	Yes	Dead 4 weeks after operation; pulmonary and femoral embolism
2	1936	Paterson, N. J...........	25	Yes	Dead 15 weeks after operation; cerebral embolism
3	1936	Philadelphia.............	22	Yes	Dead 8 weeks after operation; cerebral embolism
4	1938	Paterson, N. J...........	12	Yes	Alive and well more than 20 months after operation; see text of this paper for details
		Group 2: Unproved Cases in Which Splenectomy Was Done			
1	1918	Philadelphia.............	57	No	Improved strikingly, then died 4 weeks after operation of abscess of larynx
2	1921	Berlin, Germany.........	31	No	Alive and well for 6 months, then died of cerebral embolism
3	1921	Berlin, Germany.........	27	No	Dead 3 weeks after operation; ruptured aneurysm
4	1925	Russia..................	28	No	Alive and well at time of report, 6 months later
5	1929	Rochester, Minn.........	10	No	Dead 3 months after operation; cause unknown
6	1929	Rochester, Minn.........	37	No	Dead 7 months after operation; cause unknown
7	1935	Prague, Czechoslovakia.	21	No	Alive and well at time of report; diagnosis doubtful
8	1935	Prague, Czechoslovakia.	40	No	Dead 2 months after operation; cause unknown
9	1935	Prague, Czechoslovakia.	24	No	Dead 3 months after operation; cause unknown
10	1935	Prague, Czechoslovakia.	57	No	Dead 1 year after operation; lymphatic leukemia
11	1935	Prague, Czechoslovakia.	27	No	Dead 3 weeks after operation; cerebral embolus
12	1936	Philadelphia.............	39	No	Improved, then died 7 months after operation; cause unknown

TABLE 2.—*Preoperative and Postoperative Blood Picture in Proved Case 4*

Date, 1937	Hemoglobin, Percentage	Red Blood Cells, Millions	White Blood Cells, Thousands	Polymorphonuclears, %	Lymphocytes, %	Mononuclears, %	Coagulation Time in Minutes	Bleeding Time in Minutes	Clot Retraction	Platelets
3/18	63	3.8	7.1	62	30	8				40,000
3/22	64	3.8	6.5	68	28	4	...	....	......	32,000
3/24	..	4.1	5.9	53	43	3	5.5	Over 15	None	18,000
4/ 7	63	3.4	3.6	82	17	1	3.5	Over 15	None	35,000
4/ 9	..	...	4.6	55	44	1	...	....	......	
4/10	Splenectomy performed									138,000
4/12*	48	...	7.5	74	26	..	...	....	......	186,000
4/15	45	2.36	7.45	84	16	..	...	....	None	160,000
4/20	43	2.24	...	72	28	..	...	....		240,000
7/10	85	4.32	11.0	50	44	4	...	....	Prompt	

* A slight Arneth-Schilling shift was found on 4/12/37. No shift was found on other dates.

The Widal test for typhoid and paratyphoid bacilli gave a negative reaction.
The agglutination test for undulant fever gave a negative reaction.
The Mantoux test (intradermal injection of 1 : 1,000 dilution of tuberculin) gave a positive reaction.

The snake venom test (intradermal) gave a positive reaction after one hour.

The Wassermann test of the blood gave a 4 plus reaction. The patient's father, mother and only sister (who was older) were tested in this laboratory and in two other laboratories. All reactions were negative. Specimens of the patient's blood serum were likewise sent to two other laboratories. Both laboratories reported a plus-minus Wassermann reaction. The state laboratory reported a 3 plus Kahn reaction. The laboratory of this hospital consistently reported a 4 plus Wassermann reaction. (See section on references to false positive Wassermann reactions in cases of subacute bacterial endocarditis.)

Repeated 4 plus benzidine reactions were obtained from chemical tests of the stool. Microscopically the stool contained no ova or parasites.

The urine repeatedly gave a 1 plus reaction to the test for albumin. It contained no sugar. There were fairly numerous red blood cells and numerous hyaline and granular casts.

Roentgenograms of the teeth, taken on March 23, gave no evidence of apical foci of infection.

Roentgenograms of the chest, taken on March 27, gave no evidence of tuberculosis. The cardiac shadow was enlarged, and obliteration of the pulmonary curve indicated a mitral lesion.

Preoperative Diagnoses.—After all the laboratory data were evaluated it was concluded that the patient was suffering from a generalized infection of unknown cause. [NOTE:—The second culture of the blood, made three days prior to splenectomy, was not reported as yielding bacteria until several weeks after the splenectomy.] However, the following conditions were considered the most important possibilities: (*a*) subacute bacterial endocarditis, (*b*) acute rheumatic cardiac disease and (*c*) congenital syphilis. Associated with the condition were caries of the teeth and a laboratory type of thrombopenic purpura haemorrhagica.

Preoperative Treatment.—During March and early April conservative treatment was followed; it included: (*a*) antisyphilitic treatment, because it had not yet been established that the strongly positive Wassermann reaction was false, (*b*) transfusions of whole blood, (*c*) injection of moccasin snake venom, and (*d*) administration of sulfanilamide, salicylates and liver extract by mouth.

The patient did not improve with these measures. She seemed worse. I recommended splenectomy to the family, because I felt that it would remove a source of toxicity, because of the extremely low platelet count, because it is known that syphilis (if this was a case of syphilis) when associated with splenomegaly responds better to antisyphilitic treatment following splenectomy (Mayo [5]), because of my conviction that splenectomy is beneficial in cases of subacute bacterial endocarditis, especially when the diagnosis is unproved (I again call attention to the fact that the splenectomy in this case was performed after the culture which yielded bacteria was done but before the report came in), and because I felt that splenectomy not only would be a substitute for transfusions but would be associated with some degree of leukocytosis (the reader's attention is invited to the persistent preoperative leukopenia which prevailed in this case). Several consultations were held with various physicians, and consent for splenectomy was finally obtained, though only one other physician agreed with me that splenectomy (aside from the operative risk) offered the patient some hope for recovery.

Operation.—Splenectomy was performed by me on April 10. The operation was well borne by the patient. It took one hour and four minutes. The patient made an uneventful operative recovery and was permitted to go home on April

19. A progress note as of April 18 reads: "The patient's appearance is wan; there is evidence of wasting. The eyes, however, look rested. The lymph nodes in the cervical, axillary and inguinal areas are smaller, and this adenitis seems to be subsiding. The heart is quieter. There is no abdominal pain."

The range of pulse rate, temperature and respiratory rate during the postoperative period of hospitalization was, respectively, 88 to 120, 100.4 to 104.6 F. and 20 to 32.

Gross Pathologic Change Found at Operation.—The spleen was enlarged to four times the normal size. There were many fine adhesions between the spleen, the overlying gastrointestinal structures, the liver and the diaphragm. The liver was enlarged, extending almost down to the umbilicus on the right side, while the left lobe was adherent to the overlying diaphragm by means of fine fibrous strands. The gallbladder was not visualized. There was no fluid in the abdomen.

Pathologist's Report (Dr. Hans Wassing).—Gross pathologic picture: The spleen was markedly enlarged and weighed 12 ounces (384 Gm.). There was definite evidence of perisplenitis (in patches). There were no infarcts. The consistency was medium. Microscopic pathologic picture: Slight increase in periarterial connective tissue was visible. The pulp was cellular. Polymorphonuclear leukocytes and plasma cells were somewhat increased. Levaditi stain of splenic tissue: Spirochaeta pallida were not found. Gram stain: Streptococci were not found. Material aspirated from spleen and cultured: No growth was obtained. Culture of material from the spleen: No growth was obtained.

Summary of Other Postoperative Laboratory Work.—The first postoperative culture of the blood was made on April 19, nine days after the operation. This was reported several weeks later as yielding anaerobic streptococci. These organisms were subcultured and grown under carbon dioxide tension by Miss A. Van Saun, bacteriologist-in-charge, Paterson Board of Health, City Laboratory. Miss Van Saun reported that the organism was Streptococcus viridans.

About three months after the operation another culture of the blood was made. This was reported several weeks later as having produced no growth.

On April 19, 1937, nine days after splenectomy, this laboratory reported the Wassermann reaction as plus-minus. This was repeated three months later, at which time the report came back as doubtful plus-minus.

The blood counts may be inspected at a glance in table 2. Attention is invited to the drop in the red blood cell count and in the hemoglobin immediately after splenectomy. Since there was no hemorrhage at operation or afterward, I attribute this drop to the loss of blood which normally circulates in the splenic sinuses. It should be noted that the patient gradually recovered this loss, so that three months after the operation the red blood cell count was over 4,000,000 and the hemoglobin content was 85 per cent.

Attention is also invited to the immediate rise in the white blood cell count and to the rise in the platelet count.

Postoperative Course.—The evening temperature range continued in levels between 103 and 104 F. until April 30. After that date there was a gradual decline to normal levels, which were reached on July 1. The temperature has remained normal since that date. The patient has gained in weight from 67 pounds (30.5 Kg.) to over 100 pounds (45.6 Kg.). She is back in school and appears to be in perfect health. A recent examination of the heart revealed that it is still enlarged, and the mitral murmur is still audible, but only after exercise (the exercise consisting of stepping up and down from the seat of an adult chair).

FALSE POSITIVE WASSERMANN REACTION

Subacute bacterial endocarditis should be added to the list of diseases which may cause a strongly positive Wassermann reaction. This phenomenon has been noted before by Meyer,[10] Stokes,[11] Landau and Held,[12] Corrigan [13] and Sinnbal.[14]

SUMMARY AND CONCLUSIONS

Splenectomy has been performed in 4 cases of proved subacute bacterial endocarditis (table 1, group 1). Two of these cases were my own. In 1 of them, herein reported, the patient is alive and well more than twenty months after splenectomy. Splenectomy for the treatment of subacute bacterial endocarditis has also been performed in 12 unproved cases (table 1, group 2). In the latter group 2 patients are alive and well at the time of the report; 4 patients lived from six to twelve months. In most of the cases in both groups pain was relieved, and it was the impression of most of the attending physicians that the patients had benefited from the procedure.

False positive Wassermann reactions may be obtained in some cases of subacute bacterial endocarditis.

10. Meyer, E.: Sepsis Lenta and Positive Wassermann Reaction, München. med. Wchnschr. **74**:434, 1927.

11. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934, pp. 539 and 1056.

12. Landau, A., and Held, J.: Origin of Chronic, Nonvalvular Endocarditis, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:484, 1927.

13. Corrigan, M.: Nonspecific Wassermann and Agglutinin Reactions with Serum from Patients with Febrile Diseases, J. Infect. Dis. **41**:457, 1927.

14. Sinnbal, cited in Jadassohn, J.: Handbuch der Haut- und Geschleschtskrankheiten, Berlin, Julius Springer, 1929, vol. 15, pt. 2, p. 421.

MECHANICAL EFFECT OF ARTIFICIAL PNEUMO-PERITONEUM AND PHRENIC NERVE BLOCK

A COMPARATIVE STUDY

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I have been using artificial pneumoperitoneum for the treatment of pulmonary tuberculosis since 1931. The applicability of this method was discussed by me in previous publications.[1] The first case of pulmonary tuberculosis in which the condition was treated by the combination of phrenic nerve block and artificial pneumoperitoneum was recorded in another paper.[2] Clinical observations showed that repeated injections of moderate amounts of air into the peritoneal cavity are capable of improving the general and pulmonary condition of some patients.[3] This is of great significance, because practically all patients treated by this measure were patients for whom artificial pneumothorax had failed to produce relief, or patients who were not eligible for other types of mechanical intervention because of age, general debility, low vital pulmonary capacity or advanced stage of pulmonary involvement. Undoubtedly, some of the benefits of this treatment were due to the fact that the intestinal tuberculosis which is so often present in cases of advanced pulmonary tuberculosis was favorably influenced by pneumoperitoneum.

Favorable symptomatic response was noted early during the course of treatment in many instances. The most impressive manifestations were lessening of the severity and frequency of cough and easier expectoration. The amount of mucopurulent material the patient was able to raise from the bronchial tract with comparatively slight effort was very gratifying. The improvement in pulmonary drainage was followed by a decrease in toxicity and a gradual disappearance of constitutional symptoms, such as chills, fever, malaise, lack of appetite and loss of weight. By the decrease or elimination of cough more

1. Banyai, A. L.: Pneumoperitoneum in the Treatment of Tuberculous Enterocolitis, Am. J. M. Sc. **182**:352, 1931; Pneumoperitoneum, Dis. of Chest **3**:8 (Dec.) 1937.

2. Banyai, A. L.: Therapeutic Pneumoperitoneum: A Review of One Hundred Cases, Am. Rev. Tuberc. **29**:603, 1934.

3. Banyai, A. L.: Therapeutic Pneumoperitoneum, Tubercle **19**:176, 1938.

rest was secured for the lungs and quieter sleep for the patient. In 1 instance an otherwise uncontrollable pulmonary hemorrhage was checked by pneumoperitoneum. Coincidentally with the improved appetite, substantial gain in weight and strength was observed. In some instances, the sputum of patients who prior to treatment had had sputum persistently yielding bacteria became sterile. Continued treatment produced in some cases pulmonary clearing that was easily demonstrable on physical examination and on the roentgenogram. Roentgenologic evidence of the closure of rather large cavities was also observed.

For the purpose of ascertaining the mechanism of the empirically demonstrable beneficial effect of pneumoperitoneum for patients with pulmonary tuberculosis I have carried out a series of investigations. By measuring the distance between the apex of the lung and the highest point of the diaphragm before and after treatment I was able to prove that the diaphragm can be substantially elevated by repeated intraperitoneal injections of air.[4] It was shown that such elevation of the diaphragm compares favorably with that produced by bilateral surgical paralysis of the phrenic nerve. The present study has been undertaken in an attempt to find a more accurate gage of pulmonary relaxation.

An unselected group of 47 patients who were given artificial pneumoperitoneum treatment for pulmonary tuberculosis was studied. Of these, 12 had moderately advanced and 35 had far advanced pulmonary tuberculosis (according to the classification of the National Tuberculosis Association). The amount of air injected varied from 500 to 1,000 cc. at each treatment. The injections were given at weekly intervals in the beginning and at intervals of two weeks after pneumoperitoneum was well established. Roentgenograms of the chest were taken before and during treatment. Films were taken at the end of maximum inspiration and expiration, from a distance of 6 feet (1.82 meters; 182.8 cm.), with the patient in the upright position. The area of the right lung and that of the left lung were outlined by marking the upper margin of the apexes, the inner margin of the ribs and the dome of the diaphragm. The line separating the two lungs was drawn along the middle of the trachea and mediastinum. The area of each pulmonary field was measured by means of a planimeter, the tracer arm of which was carried along the circumference of the lung. The figures on the differential wheel of the planimeter indicated the areas in square centimeters.

4. Banyai, A. L.: Radiologic Measurements of the Apico-Basal Relaxation of the Lung During Artificial Pneumoperitoneum Treatment, Am. J. M. Sc. **196**: 207, 1938.

Measurements were made in 33 instances after the first treatment, in 1 after the second, in 7 after the third, in 4 after the fourth, in 2 after the fifth, in 7 after the sixth, in 2 after the seventh, in 2 after the eighth, in 3 after the ninth, in 7 after the tenth, in 1 after the eleventh, · in 3 after the twelfth, in 2 after the thirteenth, in 1 after the fourteenth, in 4 after the fifteenth, in 6 after the sixteenth, in 4 after the nineteenth, in 2 after the twentieth, in 3 after the twenty-first, in 4 after the twenty-second and in 1 after the twenty-third. These represent 99 instances with films taken at maximum inspiration and at maximum expiration (and with separate measurement of the right and left lung). Including measurements of the roentgenograms studied before treatment, 584 measurements were made and analyzed.

The patients were divided into two groups. The first group included patients in whom one lung was more diseased than the opposite lung. The second group comprised patients with about equal involvement on both sides. After the first treatment the following results were found in the first group. There was no reduction in the surface area of the more involved lung on inspiration in 8 and on expiration in 8; reduction was noted in 19 on inspiration and on expiration. The maximum reduction of the surface area was 14 per cent of its original extent on inspiration and 13 per cent on expiration. Reduction was absent on the "good" side on inspiration in 5 instances and on expiration in 10; reduction was noted on inspiration in 22 and on expiration in 17. The maximum decrease was 15 per cent on inspiration and 23 per cent on expiration. For patients with about equal involvement on the two sides the maximum reduction on inspiration was 8 and 10 per cent on the right and left side, respectively, and on expiration 7 and 5 per cent, respectively. In 4 instances on inspiration and in 4 instances on expiration no reduction was noted. Table 1 gives the maximum extent of reduction of the surface area after a gradually increased number of treatments. The figures represent the highest percentage by which the preoperative surface area was reduced. Of the 33 patients studied after the first injection, repeated measurements were taken for 25 on subsequent occasions during the more advanced stages of the treatment. All patients in whom no decrease of the surface area was produced by the first injection showed decrease on subsequent injections. Table 2 gives the number of instances in which the surface area was reduced and the number of cases in which no reduction was observed.

A comparison was made between the extent of reduction of the surface area in patients with a well established pneumoperitoneum, that is, in patients who had had ten or more treatments, and that in a group of 30 patients treated by surgical paralysis of the phrenic nerve.

In the latter group the maximum reduction was 27 per cent on inspiration and 25 per cent on expiration, whereas in the cases in which pneumoperitoneum had been established the maximum reduction on the more diseased side was 36 per cent on inspiration and 35 per cent on expiration. The average reduction after surgical paralysis of the phrenic nerve was 11.7 per cent on inspiration and 7.9 per cent on expiration, whereas for patients with well established pneumoperitoneum the corresponding averages were 13.5 and 15.6, respectively. These figures

TABLE 1.—*Maximum Reduction of Roentgenologic Surface Area* *

Number of Treatments	More Diseased Lung		Less Diseased Lung		About Equal Extent of Disease			
					Right Lung		Left Lung	
	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration	Inspiration	Expiration
1	14	13	15	23	8	7	10	5
2	10	15	6	13	..	..	..	..
3	14	10	13	13	6	0	8	3
4	4	11	9	10	..	..	..	..
5	18	17	8	13	..	..	..	..
6	8	13	15	22	16	20	13	8
7	18	13	12	14	..	..	..	..
8	17	24	3	11	..	..	..	..
9	14	13	16	13	..	..	..	..
10	24	13	19	14	..	..	..	..
11	..	..	..	..	12	2	8	6
12	18	24	28	27	..	..	..	..
13	34†	50†	11	23	..	..	..	..
14	9	7	5	7	..	..	..	..
15	11	23	16	23	..	..	..	..
16	20	20	22	26	..	..	..	..
19	36	33	18	46	..	..	..	..
20	14	26	27	35	..	..	..	..
21	10	22	20	28	..	..	..	..
22	25	21	26	19	..	..	..	..
23	18	10	10	21	..	..	..	..

* The figures indicate the percentage by which the pretreatment surface area was reduced.
† Combined with phrenic nerve block.

show that it is possible to produce a greater reduction of the roentgenologic surface area by artificial pneumoperitoneum than by phrenic nerve block.

Assuming that the decrease in the roentgenologic surface area reflects the degree of pulmonary relaxation induced by mechanical measures and that the relaxation of the tuberculous lung is the most important therapeutic factor, it is obvious that in this respect artificial pneumoperitoneum is superior to phrenic nerve block. Additional advantages of pneumoperitoneum over phrenic nerve block are: (1) It is a reversible operation that can be adapted to the individual case or discontinued at any time during treatment; (2) the relaxation of the lung is induced gradually so that a sudden reduction of the vital capacity is avoided; (3) it causes relaxation of the "good" lung and thereby protects it against

TABLE 2.—*Number of Instances of Reduction of the Roentgenologic Surface Area*

Number of Treatments	More Diseased Lung				Less Diseased Lung				About Equal Extent of Disease — Right Lung				Left Lung				Measurements After Treatments
	Inspiration	Expiration	Absent Inspiration	Absent Expiration	Inspiration	Expiration	Absent Inspiration	Absent Expiration	Inspiration	Expiration	Absent Inspiration	Absent Expiration	Inspiration	Expiration	Absent Inspiration	Absent Expiration	
1	10	19	8	8	22	17	5	10	5	3	1	3	4	4	3	1	132
2	1	1			1	1		3									4
3	3	2	3	4	5	3	1	3	1	3	1	1	1				28
4	4	4			4	3											16
5	1	2	1		2	2				1							8
6	4	4		1	4	4		2		1		1		1			28
7	2	2			2	1	1		1				1				8
8	1	4	1		1	2											8
9	3	2			2	2	1		1	1	1		1		1		12
10	6	3		1	7	3			1				1	1			28
11		6				5											4
12	2				2	2								1			12
13	2	2			2	2							1				8
14	1	3	1		1	1							1				4
15	3	6			3	3											16
16	6	4			5	5											21
19	4	2			4	4											16
20	2	3			2	2											8
21	3	6			3	3											12
22					4	4											16
23					4												4
Total	71	72	14	13	77	67	8	18	13	9	1	5	12	12	3	1	396

the spread of the disease by aspiration from the opposite side; moreover, the relaxation of the "good" lung with its consequent passive hyperemia creates an unfavorable site for the development of metastatic tuberculous foci; (4) by elevating the diaphragm and supporting it in a bracelike fashion during coughing spells, pneumoperitoneum makes coughing easier, more efficient and more productive, whereas paralysis of the phrenic nerve is sometimes followed by the opposite effect; (5) by virtue of the elevation of both domes of the diaphragm, pneumoperitoneum creates a favorable condition for the healing of tuberculosis in both lungs, while simultaneous phrenic nerve block for the treatment of bilateral tuberculosis is not an accepted or a feasible operation; and (6) the curative influence of pneumoperitoneum on tuberculous enterocolitis is likely to improve the patient's ingestion and digestion, and thereby it is likely to improve his general condition, the immunity of his tissues, his resistance and his capacity for repair.

The degree of relaxation of the more involved lung was compared with that of the less involved or "good" lung. It was noted that for patients with well established pneumoperitoneum, that is, patients who had had ten or more treatments, the inspiratory reduction of the surface area on the more diseased side was greater than on the opposite side in 20 and smaller in 10; there was no reduction in 1 case, and reduction was equal on the two sides in 3. The expiratory reduction was greater on the more involved than reduction was on the less involved side in 14 cases and smaller in 16; reduction was absent in 2 and equal on the two sides in 2. Extensive pleuropulmonary adhesions, rigidity of the lung tissue caused by long standing fibrosis and contraction of the thorax were responsible for the absence of or the rather insufficient pulmonary relaxation in some cases.

An analysis of the relation between the reduction in inspiration and that in expiration in all instances showed the following data: On the right side the inspiratory decrease was greater than the expiratory in 44 instances and smaller in 42 instances; decrease was absent in 8 cases, and the values were equal in 5. On the left side, the inspiratory decrease was greater than the expiratory in 40 instances and smaller in 36; decrease was absent in 18 cases, and the values were equal in 5.

Although I am aware of the fact that two-dimensional measurements do not accurately gage changes of a three-dimensional object, such as the lung, this method is a sufficient approximation of the problem and has long been generally accepted in studies on artificial pneumothorax. Pulmonary relaxation by artificial pneumoperitoneum, as I stated before,[5] is dependent on the tonicity and integrity of the diaphragm, the tonicity

5. Banyai, A. L.: Pneumoperitoneum for the Treatment of Pulmonary Tuberculosis, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, to be published.

of the abdominal wall, the type of breathing, the pathologic changes in and surgical status of the lung and the amount of air injected.

The measurements presented in this study prove that it is possible to produce a therapeutically satisfactory relaxation of the lung by artificial pneumoperitoneum. Relaxation implies a reduction of the elastic tension of the lung; this, in turn, facilitates the closure and healing of cavities. The lymph stasis in the relaxed pulmonary tissues stimulates fibrosis. The passive congestion and the increased content of carbon dioxide associated with relaxation create unfavorable conditions for the tubercle bacilli and accelerate the healing process.[6] On the basis of previous clinical investigations[7] I wish to emphasize again that in artificial pneumoperitoneum treatment, as in pneumothorax treatment, adequate relaxation of the lung is a far more important factor in healing than is immobilization. The combination of surgical paralysis of the phrenic nerve on the more involved side with pneumoperitoneum was conducive to gratifying results in my practice. It is evident that a paralyzed, flaccid diaphragm rises higher under the influence of pneumoperitoneum than does an intact diaphragm. Except when the diaphragm is fixed by heavy adhesions, remarkable pulmonary relaxation can be observed in this combined method.

CONCLUSION

Data presented in this study are based on 584 roentgenographic measurements.

It has been found that a well established artificial pneumoperitoneum is likely to cause a substantial reduction of the roentgenologic surface area of the lung and, presumably, a therapeutically satisfactory pulmonary relaxation.

Adequate pulmonary relaxation is the fundamental factor in the healing of turberculous lesions of the lung.

Empiric observations, such as the clearing of extensive lesions, checking of otherwise intractable hemorrhage and closure of large cavities in patients who were unable to take other types of mechanical treatment, postulate the attainment of sufficient pulmonary relaxation by this method.

During effective pneumoperitoneum treatment the maximum as well as the average decrease in the roentgenologic surface area of the lung was greater than that found after surgical paralysis of the diaphragm.

In these observations an explanation of the beneficial effects of this treatment is given. Because of its effectiveness and its simplicity of technic, artificial pneumoperitonuem is recommended as a useful procedure for the treatment of certain types of pulmonary tuberculosis.

6. Banyai, A. L.: Carbon Dioxide Inhalation in Pulmonary Tuberculosis, Am. Rev. Tuberc. 30:642, 1934.

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PHYSICAL AND TOXIC FACTORS IN SHOCK

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The word shock as currently used covers essentially the following conditions:

1. Primary shock, characterized by direct reduction of blood pressure and other less precisely defined acute symptoms, attributed to nervous, circulatory or toxic causes.

2. Secondary shock, a more slowly developing condition, of better defined character but of disputed etiology. It has usually been produced experimentally by mechanical, thermal or other trauma of the limbs or of the intestine. Authorities are agreed as to the epochal importance of the physical concept, established by Phemister,[1] Blalock[2] and their collaborators and corroborated by numerous writers (Herbst,[3] Holt and Macdonald,[4] Harkins[5] and his collaborators, Underhill[6] and his collab-

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From the Polyclinic Hospital.

1. Phemister, D. B., and Handy, J.: J. Physiol. **64**:155-173, 1927. Phemister, D. B., and Livingstone, H.: Ann. Surg. **100**:714-727, 1934. Parsons, E., and Phemister, D. B.: Surg., Gynec. & Obst. **51**:196-207, 1930. Phemister, D. B.; Roome, N. W., and Keith, W. S.: ibid. **56**:161-168, 1933.

2. (*a*) Blalock, A.: Influence of Exposure to Cold and of Deprivation of Food and Water on the Development of Shock, Arch. Surg. **29**:1055-1068 (Dec.) 1934; (*b*) Internat. Clin. **1**:144-161, 1933. (*c*) Blalock, A., and Levy, S. E.: Am. J. Physiol. **108**:734-738, 1937. (*d*) Blalock, A., and Brooks, B.: Ann. Surg. **100**:728-733, 1934. (*e*) Beard, J. W., and Blalock, A.: J. Clin. Investigation **11**:249-265, 1932. (*f*) Daniel, R. A., Jr.; Upchurch, S. E., and Blalock, A.: Surg., Gynec. & Obst. **56**:1017-1020, 1933.

3. Herbst, R.: Arch. f. klin. Chir. **176**:98-122, 1933; Wien. klin. Wchnschr. **47**:868-871, 1934.

4. Holt, R. L., in Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**:1473-1479, 1935. Holt, R. L., and Macdonald, A. D.: Brit. M. J. **1**:1070-1072, 1934.

5. Harkins, H. N.: Experimental Burns: I. The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns, Arch. Surg. **31**:71-86 (July) 1935; Proc. Soc. Exper. Biol. & Med. **32**:432-434, 1934. Harkins, H. N., and Hudson, J. E.: ibid. **32**:434-435, 1934. Harkins, H. N., and Harmon, P. H.: Surgery **1**:276-281, 1937. Harkins, H. N.; Harmon, P. H., and Hudson, J. E.: Lethal Factors in Bile Peritonitis: "Surgical Shock," Arch. Surg. **33**:576-608 (Oct.) 1936. Harmon, P. H., and Harkins, H. N.: Peritonitis: Effect on Blood Pressure of Peritoneal Content in Suppurative and in Bile Peritonitis, ibid. **34**:565-579 (April) 1937: Peritonitis:. Effect on Blood Pressure of Protein-Free Extracts of Peritoneal Content and of Filtrates from Pure Cultures of Bacteria, ibid. **34**:580-590 (April) 1937.

orators, Roome and Wilson,[7] Aikawa [8] and others) through demonstration of a passage of protein-containing fluid resembling blood plasma into the injured tissues, with consequent increase of corpuscle counts and reduction of volume of the blood. The opposite and older doctrine of a toxic or nervous origin has been abandoned as a sole explanation of secondary shock and is questioned even as a supplementary theory, though Cannon [9] and Dale [10] have stated their continued belief in such a factor and it has been championed in recent researches by Slome,[11] Moon and Kennedy,[12] Coonse [13] and his collaborators and others.

The earlier literature is sufficiently reviewed by Boyers,[14] Cannon [9] and the other authors cited.

Recently Dragstedt and Mead [15] have furnished apparently conclusive proof of the absence of any important amount of hypotensive substance in the blood of dogs after mechanical trauma of muscles. On the other hand, Rosenthal [16] is said to have demonstrated a substance resembling but not identical with histamine in the blood of animals after burns of the skin.

Histamine has held the place of chief interest in the chemical study of shock, and in this connection reference should be made particularly to the work of the Lewis-Barsoum group.[17] Lewis and Barsoum dem-

6. Underhill, F. P.; Carrington, G. L.; Kapsinow, R., and Pack, G. F.: Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment, Arch. Int. Med. **32**:31-49 (July) 1923.

7. Roome, N. W., and Wilson, H.: Proc. Soc. Exper. Biol. & Med. **32**:400-401, 1934.

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9. Cannon, W. B.: (*a*) Traumatic Shock, New York, D. Appleton and Company, 1923; (*b*) Ann. Surg. **100**:704-713, 1934.

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11. Slome, D., in Discussion on Traumatic Shock, Proc. Roy. Soc. Med. **28**: 1479-1493, 1935.

12. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14**: 360-371 (Sept.) 1932; J. Lab. & Clin. Med. **19**:295-301, 1933. Moon, V. H.: Ann. Int. Med. **8**:1633-1648, 1935.

13. Coonse, G. K.; Foisie, P. S.; Robertson, H. F., and Aufranc, O. E.: New England J. Med. **212**:647-663, 1935.

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16. Rosenthal, S. R., cited by Fantus, B., and Dyniewicz, H. A.: Compound Solution of Tannic Acid, J. A. M. A. **109**:200-203 (July 17) 1937.

17. Lewis, T., and Grant, R.: Heart **12**:73-120, 1925. Barsoum, G. S., and Gaddum, J. H.: Clin. Sc. **2**:357-362, 1936. Barsoum, G. S., and Smirk, F. H.: ibid. **2**:337-352 and 353-355, 1936.

onstrated with apparent positiveness that the phenomena of reactive hyperemia following circulatory occlusion in limbs must be due to some substance which diffuses only very slowly from its site of formation in the tissues into the blood. Barsoum and Smirk furnished evidence that true histamine or a histamine-yielding substance is increased in the blood as a result of stoppage or slowing of the circulation. They at least partially answered the objection regarding diffusibility by showing that the substance in question is held in the tissues and red corpuscles in far larger amounts than in the plasma, but it causes capillary dilatation and other typical effects only when its concentration rises in the plasma. Increase of histamine or the substance yielding it was also found in the blood of patients with extensive cutaneous burns, and the degree of this increase was approximately in proportion to the extent of the burns. On the other hand, it was not possible to correlate these chemical findings with shock symptoms or any other features of the clinical course. Up to the present, a chemical explanation of shock has not been furnished by the researches on histamine or any other substance.

Aside from surgical conditions, shocklike states are recognized medically in two principal forms: (*a*) shock occurring as a more or less acute effect of a variety of poisons, particularly histamine, bacterial products and some organ extracts, and (*b*) shock occurring as a late complication in many states of prostration or circulatory failure, which entail some degree of tissue asphyxia by reason of inadequate blood flow or possibly also direct toxic damage of the tissues or vessels. Among these states is the late, severe stage of diabetic acidosis. This observation was made possible only by the introduction of insulin, which was able to clear up the associated factors, and I was the first to state the fact that "when too long a time elapses the patient reaches a fatal stage, in which strenuous treatment may clear up sugar and acetone and raise the blood alkali, but death nevertheless occurs with symptoms resembling shock."[18] Also Wishart and I[19] first observed that dogs into which different "acetone bodies" were injected displayed only moderate symptoms of drunkenness while the poison was circulating but after its disappearance from the blood they died from increasing prostration of undefined character. Peters and his associates[20] found indications of some passage of fluid from the blood into the tissues in the presence of severe diabetic acidosis. This is in harmony with the shock

18. Allen, F. M.: Ann. Int. Med. **2**:210, 1928.

19. Allen, F. M., and Wishart, M. B.: J. Metab. Research **4**:613-648, 1923.

20. Peters, J. P.; Kydd, D. M.; Eisenmann, A. J., and Hald, P. M.: J. Clin. Investigation **12**:297-326, 1933. Peters, J. P.; Kydd, D. M., and Eisenmann, A. J.: ibid. **12**:355-376, 1933.

hypothesis.[21] Several workers have tried transfusions in the treatment of acidosis, according to current views of shock therapy, but without particularly striking results. It remains probable that any further advance in the treatment of coma must be along some line outside the ordinary routine for patients with diabetes and probably must be related to the problem of shock.

The established methods of investigating shock are open to certain criticisms. Experiments with perfusion encounter objections because of the small quantity of toxic material that may be contained in the circulating blood and the power of tissues to neutralize or destroy such material; thus it is difficult to demonstrate the nature of uremia by means of such experiments. Maintenance of arterial stasis for a few minutes, as used by Phemister and Handy,[1] is too brief to allow much accumulation of shock-producing substance. Tissue extracts may not contain sufficient amounts of the true toxin or may contain post-mortem products. The usual traumatic experiments involve complications of injuries to the nervous system and also necrotic tissue and blood clot. Proof of the physical hypothesis does not disprove the existence of other factors than fluid migration and, furthermore, does not show the cause of the fluid migration. The prevailing uncertainty seems to make any innovation in the mode of attack highly desirable.

Shock resulting from asphyxia of a sufficient mass of tissue for a sufficient length of time has long been familiar to surgeons and received the notice of the Shock Committee during the World War. For example, Cannon [9a] described the case of an unwounded man who suffered merely a compression of the thigh between fallen timbers for twenty-four hours and who went into shock after being released and died in thirty-two hours. A case report by Panella [22] is similar. Experimental ligations have also been performed by Cannon, Donati,[23] Paolucci,[24] Fogliani [25] and others, with twofold results: viz., shock is

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21. To guard against confusion (Atchley, D. W.: Bull. New York Acad. Med. **10**:138-150, 1934; New England J. Med. **213**:861-868, 1935), simple, precise definitions of a few fundamentals are essential. 1. Hemorrhage is loss of circulating fluid and corpuscles. 2. Dehydration is loss of fluid externally and is overwhelmingly the predominant process in the presence of cholera and of diabetic acidosis. 3. Secondary shock involves loss of fluid from the circulation into the tissues, even if the total body fluid is unchanged or increased. The radical physiologic difference is illustrated by the pyrexia of severe dehydration and the subnormal temperature of severe shock. Though the three conditions necessarily sometimes merge or lead into one another, progressive authors strive for clear differentiation, since the distinctions are important both theoretically and therapeutically.

22. Panella, P.: Ann. ital. di chir. **14**:1-14, 1935.

23. Donati, M.: Arch. ital. di chir. **12**:1-22, 1925.

24. Paolucci, R.: Arch. ital. di chir. **21**:329-344, 1928.

25. Fogliani, U.: Riv. di pat. sper. **9**:257-277, 1932.

applied to one hindleg of a rat as high as possible against the body. The pressure should be sufficient to assure absence of bleeding from incisions in the leg or from the femoral artery below the ligature, but not so extreme as to create unnecessary complications, such as thrombosis or ulceration (which require rejection of the experiment). The animal is then confined in an individual box which keeps it helpless but comfortable, with precautions against chilling. Dehydration may vary from a slight to a considerable degree. The body weight of a rat weighing 150 Gm. may fall by 10 to 25 Gm. The red blood cell count may rise by as much as 1,000,000 in five or six hours and by 2,000,000 or more if the ligation is of longer duration. Nevertheless, there is no death or serious weakness of a healthy rat during ligation, even if constriction is maintained for fifteen hours or longer. On release after a five-hour ligation the rat appears entirely vigorous; then increasing symptoms of secondary shock, in the form of subnormal temperature, dyspnea and weakness, lead to death. Strong animals are more resistant than weak ones. Old, fat rats (because of the greater mass of tissue in the thigh or because of age) are often less resistant than young, thin ones. The most important factor is the actual height of the ligature, that is, whether it remains close against the body or slips down more or less. With allowance for such variations, the degree of shock produced by three hours' ligation of one entire leg is never sufficient to kill. Ligation for four hours is often fatal, and ligation for five hours is regularly fatal.[27]

These conditions may be altered in two ways, namely extensively (by variations in the amount of tissue ligated) or intensively (by variations in duration of ligation). As an example of the former, the ligation of both entire hindlegs for three hours may be fatal; or if continued for five hours, it causes death within from three quarters of an hour to three hours after release of the ligatures, instead of the three to six hours which is usual after ligation of one leg. Increased duration intensifies the effect so that fatal shock occurs from ligation of a smaller mass of tissue. One of these factors may be used to counteract the other; for example, ligatures applied at or below the middle of the calf involve too little tissue for fatal shock. Such ligations are therefore the only ones suitable for determining the actual duration of local asphyxia which can be tolerated without the occurrence of gangrene. This is longer than commonly supposed, viz., about twelve hours for the rat and fifteen hours, or possibly more, for the dog or the cat, at ordinary room temperature.

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27. Recently, with rats from another source, it has been necessary to use six hours of ligation for uniformly fatal results. It may, therefore, be necessary to establish a standard for each particular strain of rats.

Reactive hyperemia and edema have been described by former writers; and, as observed by Blalock[2] and Holt,[4] the accumulation of fluid is not limited to the ligated area but commonly extends beyond the leg, sometimes well up over the groin or the abdomen.

Since all the phenomena of secondary shock can be produced under these fairly exact and uncomplicated conditions, the method seems well suited for studying the cause or mechanism of shock. Pain and other nervous factors are eliminated, partly by the relative painlessness of the procedure and partly by the anesthesia and nerve block produced by the ligation itself. The experiments were therefore performed without anesthetics, except as specifically mentioned.

BLOOD COUNTS AFTER LIGATION

Counts were taken sometimes before application of the ligature, always just before its release and at selected intervals afterward. The blood was obtained routinely by clipping the end of the tail. In some cases of shock in which the tail yielded no blood and in other instances for comparative purposes, blood has been taken from the heart, from a jugular or femoral vein or from an artery of the leg. While the variations in different vascular tracts might be instructive for some detailed studies, the general course of dilution or concentration is shown in the same way regardless of the source of the blood. In the first part of the work, large numbers of leukocyte counts were included, which showed sometimes a relation with the concentration or dilution of the red cells but also numerous fluctuations which were meaningless for the present purpose. Hemoglobin determinations merely corroborated the red cell counts; therefore, usually only the latter were taken.

It is unfortunate that the restricted conditions under which these experiments were performed precluded determinations of blood volume, blood pressure and other important data. On this point, however, there is the complete demonstration by former writers that the rising corpuscle count is a sign of increased blood concentration, connected with loss of plasma and decrease of total blood volume.

Since the experiments were necessarily so simple and the data consist of nothing but hundreds of blood counts, it is possible to state the results summarily so as to save the space and expense of charts and protocols. Any points which may seem doubtful can be easily verified by any one interested. The basic condition is that which has been described by former authors for other species of experimental animals; namely, from a level of about 8,000,000 red cells at the end of ligation (ranging possibly from 7,000,000 to 9,000,000 according to the species and the special circumstances) the count rises steadily after release to a level of 10,000,000, 11,000,000 or 12,000,000 at death. The visibly

dark, thick character of the blood, the emptiness of all superficial blood vessels and the scanty flow even in such large veins as the femoral and jugular, occurring in parallel with the increasing local transudation of fluid and the symptoms of general prostration, conform to the full specifications of the physical hypothesis of secondary shock.

As living animals cannot be standardized as precisely as chemical reactions, exceptions and gradations occur under the aforementioned rules and are explained principally by the variable factor of constitutional strength. Animals which are weak from any cause, such as youth, age, exhaustion or intercurrent disease, are sensitive to shock in proportion to their weakness, while exceptionally strong animals have correspondingly high resistance. Several observations were made to learn whether the weak animal is unable to maintain its blood volume as efficiently as a normal animal or whether it dies from smaller changes in the blood. Ligations of limbs were found to affect the red cell counts similarly for weak animals and strong animals, but the weak ones were less able to endure the change, so that they died at an earlier stage when the erythrocyte count had risen by 2,000,000 or sometimes by only 1,000,000.

COMPARISON WITH PRIMARY SHOCK

Attempts were made to compare the blood changes of secondary shock with the effects of trauma supposed to produce primary shock. As the small size of rats renders them highly susceptible to dehydration, temperature and other influences, these experiments have all been duplicated with cats, and conclusions have been drawn chiefly from experiments with the latter. The following procedures have been used:

With the animals under amytal narcosis, nerve trunks have been dissected out (beginning at the ankle) and stimulated repeatedly by pinching and cutting from below upward in the course of several hours, until both sciatic trunks have been used up to their point of origin.

In the same or other animals, the spinal cord has been successively crushed at different levels, from its lower end to the upper thoracic region. Other animals have been kept unconscious by a series of blows on the skull.

Animals either under anesthesia or with the spinal cord divided have been subjected to bloodless traumatization of limbs or viscera, with the endeavor to avoid any marked local edema or secondary shock during this time. For example, a cat, after brief etherization for division of the spinal cord, appears entirely well except for paraplegia. One hindfoot is then amputated bloodlessly. After perhaps fifteen minutes, compression is applied to squeeze most of the blood out of another zone of tissue, and a slightly higher amputation is performed, several interlocking mass ligatures being applied to block all blood supply before the tissues are divided. These successive procedures in the course of several hours lead finally to the amputation of both hindlegs at the hips, with all connecting muscles. The cat shows no sign of pain, and each zone of tissue is removed before there is time for the preceding operation to produce much edema in it.

Blood counts taken during any of these experiments with primary shock, continued over a period equal to that occupied by experiments with secondary shock, have never shown any marked or consistent changes resembling those of secondary shock. Since the two conditions are recognized as radically different, it is questionable whether the name shock should continue to be applied to both.

Possibly the prevention of pain also serves largely to prevent shock in such experiments. But there may even be suggested a need for differentiation of the effects of certain lesions of the nervous system and tissues now lumped together under primary shock. Apparently, the sufficiently extensive mutilation of denervated tissues can cause delayed death which is not identical with death from secondary shock. It was not possible to determine in this work whether such a death is due to familiar or to unknown factors.

RESULTS OF AMPUTATION AFTER LIGATION

Regardless of the duration of ligation (up to fifteen hours or longer) if amputation is performed instead of release of the ligature, none of the phenomena of secondary shock occur. Even when both hindlegs have been subjected to prolonged ligation, the immediate amputation of both allows the animal to survive. These principles are well understood and are followed in operations on man.

When one hindleg of a rat has been ligated for five hours, amputation will still save life if performed within a variable time (the limits being about one to three hours in numerous observations) after release of the tourniquet. This is a period within which the clinical symptoms and also the rise of the blood count are still well below the maximum. If further time is allowed, until the animal has passed into a more severe stage of shock, life can no longer be saved by amputation.

These results are explainable under either the toxic or the mechanical hypothesis. Under the former the ligated leg is assumed to be a source of poison for the organism, and under the latter it is viewed as the site of fatal transudation of fluid. A nervous cause is excluded, partly by the results of amputation and partly by the complete motor and sensory paralysis which follows prolonged ligations of the legs of rats.

RESULTS OF BLOOD TRANSFUSION

Blood for transfusion is drawn from the heart into a syringe containing heparin in powder or strong solution. The animal in a condition of shock is often quiet enough to receive the injection with little restraint, but sometimes the usual veins (tail and leg) are too empty to be entered by puncture through the skin. It then becomes necessary

to etherize for injection into the exposed jugular vein, but the entire procedure occupies only a few minutes, and the rat awakens quickly without apparent harm.

For rats weighing 100 to 200 Gm., after ligation of one hindleg for five hours transfusion of 4 to 8 cc. of fresh blood ordinarily saves life within about the same time limits as amputation. Transfusion fails to save under three conditions: (1) after the lapse of too long a time following release of the tourniquet; (2) after too extensive injury, e. g., after prolonged ligation of two or four legs or of the abdominal aorta; and (3) after too intensive injury, e. g., after ligation of one hindleg for seven to twelve hours.

Under any of these conditions, however, the reviving effect of transfusion should be noted. Death from this form of shock invariably occurs by apnea, while the heart may continue to beat rather vigorously for periods varying from a few seconds up to a minute or more. This fact is in agreement with the accepted view that secondary shock is not due to failure of the circulatory organs. When respiration has definitely stopped, no matter how strongly the heart may be beating, it has never been possible in a single instance to revive the animal by transfusion or to restore respiration (for more than a few seconds or minutes) by any of the drugs or treatments in ordinary medical use. But when the rat is literally at its last gasp and in imminent danger of dying before the vein can be entered, the transfusion usually brings about an immediate spectacular improvement. Under the fatal conditions enumerated this revival is temporary; the subnormal temperature is not elevated, and extreme weakness quickly or slowly returns. Sometimes a second transfusion may give slighter benefit, but a state is soon reached in which neither transfusion nor anything else helps. The net result, therefore, is only a brief prolongation of life, ranging perhaps from half an hour to three or four hours.

The reviving effect of the transfusion can be logically explained under the physical or mechanical hypothesis as due to replenished blood volume and consequently to improved circulation. The ultimate fatality also appears explainable under this hypothesis, as follows. As regards the first condition, when the animal has reached too extreme a stage after the lapse of too long a time, this hypothesis takes cognizance of the secondary constitutional changes which have been proved to occur in the presence of advanced shock and which are necessarily fatal after they have reached a certain degree. As regards the second and third conditions, namely, the more intense injury of a given mass of tissue or the injury of a greater mass, it may be assumed that the transudation of fluid is increased, as was actually demonstrated by Wilson and Roome.[26a] In this event there may be temporary help from transfusions,

but plasma may continue to be lost until finally the circulation may be clogged with a plethora of corpuscles, and death inevitably follows.

This assumption has been tested in numerous experiments with both the second and the third condition. The amount of blood given has varied from 4 to 18 cc., the larger amounts being divided into several injections. When such transfusions are begun shortly after or even before the release of the ligature and are continued with every conceivable variation of quantity and interval, life may be prolonged by a maximum of a few hours but is never actually saved under the conditions of severe shock as mentioned. The red cell count always shows a definite increase, commonly ranging between 11,000,000 and 14,000,000, while at the same time the usual emptiness of the peripheral veins is replaced by visible distention, and at autopsy the heart and the great veins are observed to be engorged. These conditions are in accord with the supposition of an increase of corpuscles and of blood volume together with a loss of plasma.

Tests for the presence of a circulating toxin have also been made by withdrawing blood from the hearts of rats either shortly before or immediately after death from this form of shock. All the results described for transfusion of normal blood are reproduced by transfusions of "shock blood." The reviving effect is the same; a rat in the very act of dying from shock can be restored by the blood of rats which have died from shock in the same manner as by normal blood, even though the "shock blood" is thick and dark and has not been oxygenated or otherwise treated. The prolongation of life is the same whether normal blood or "shock blood" is used, and owing to individual variations it may happen that some rats receiving "shock blood" outlive some that received normal blood, in spite of the higher corpuscle and lower plasma content of the "shock blood." From these observations it seems clear that the important element in the effect of transfusions is the increased volume of the circulating medium, and that the hypothetic toxin cannot be present in more than trivial amount in the quantity of blood transfused.

RESULTS OF INJECTION OF CORPUSCLES

Corpuscles were obtained by moderate centrifugation of heparinized blood, after one or two washings with saline solution or, more often, without washing. The mass obtained was capable of flowing easily through the 26 or 27 gage needle used for all the transfusions. Experiments were performed with injections of these corpuscular sediments in various quantities and at various intervals after release of the tourniquet. The quantity tolerated is naturally less than for whole blood. Revival of dying rats may be observed to a slight extent but is often

lacking. The period of survival at best is much shorter than with whole blood, and too large or too frequently repeated injections are actually fatal. If one disregards the meaningless counts obtained when rats died almost immediately after the injection, the increase of corpuscles in rats surviving for any considerable time did not rise much above 14,000,000. All these observations accord with the idea of the importance of the physical factor of concentration of the blood and loss of plasma.

RESULTS OF INJECTION OF PLASMA

If secondary shock consists in an escape of blood plasma or a fluid closely resembling it from the vessels into the tissues, the optimum relief should logically be afforded by a restoration of plasma, as postulated by Rukstinat,[28] by Good, Mugrage and Weiskittel [29] and by most supporters of the physical hypothesis. Various experiments were performed, different amounts of tissue being ligated. In one form, 1 rat was given a transfusion of a certain amount of heparinized blood, while an equal quantity was centrifuged and divided between 2 similar rats, 1 being given the corpuscles and the other the plasma. Another plan was merely to inject plasma in the same quantities (totals of 5 to 20 cc.) at intervals, as previously described for whole blood.

For the revival of rats at the point of death from shock, the plasma (not oxygenated or otherwise prepared) was decidedly inferior to whole blood. The effect, if obtained, was slight or brief, and death sometimes actually occurred during the injection. The theoretic expectation, therefore, that plasma would produce particularly beneficial effects by filling up the circulation, reducing the high concentration of corpuscles and diminishing the viscosity was by no means fulfilled with animals in this extremely late stage of shock.

In other experiments, smaller or larger injections of plasma were given at intervals beginning either just before or soon after the release of the tourniquet, in the attempt to prevent the development of the fatal stage. The standard preparation for the majority of these experiments consisted in high ligation of both hindlegs for five hours. Three gradations of injections of plasma were then tried. In group 1 the smallest possible quantities of plasma were given (three or four injections of 2 to 4 cc. each), not preventing the concentration of blood altogether but merely keeping the corpuscle counts within the supposedly safe limits of 9,000,000 to 10,000,000 cells, the purpose being to minimize any possible harm that might be done by the injections of

28. Rukstinat, G. J.: Experimental Study of Traumatic Shock, Arch. Path. **14:**378-400 (Sept.) 1932.

29. Good, R. W.; Mugrage, R., and Weiskittel, R.: Am. J. Surg. **25:**134-139, 1934. Good, R. W., and Boyer, B. E.: J. Med. **12:**630-636, 1932.

plasma. In group 2 intermediate amounts of plasma were injected under the guidance of corpuscle counts so as to keep the concentration of the blood as nearly normal as possible from beginning to end; and in several such experiments there was success in preventing the red cells from varying more than half a million at any time. In group 3, the attempt was to overcompensate, with three to four injections of 5 to 10 cc. of plasma, so as to keep the blood constantly diluted to various degrees and to have a surplus of fluid always available for transudation.

For such a study the advantages of the ligation method are obvious, as compared with the production of shock by any means involving hemorrhage, neural lesions or the presence of masses of dead or dying tissue. Wilson and Roome's [26a] observation of the increased amount of transudation is easily confirmed, but any such increase can be amply covered by the quantity of plasma injected. It is readily understood, as shown by several authors, that when a severe reduction of blood pressure and increased blood concentration are allowed to continue for several hours the secondary disturbances are such as to prevent recovery. The advantage of the present method is that compensation for these changes can be introduced from the outset.

Under any of the three plans mentioned the circulation is sufficiently well maintained to permit of obtaining samples of blood from the tail at all stages. The third method creates visible overfilling of the superficial vessels and can be carried to the point of obviously fatal hydremic plethora. Even with this plethoric death and engorgement of the heart and the great veins at autopsy, the end still comes with apnea rather than with stoppage of the heart.

Rats with severe shock, given suitable injections of plasma from the outset, live decidedly longer than untreated controls and apparently a little longer than rats given transfusions of whole blood. The greater edema in the ligated legs is due at least partly to the longer time. The general symptoms and course of the shock are retarded but not essentially altered. The point is soon reached at which the rat with a normally maintained blood count or with a reduced blood count and appearances of increased blood volume is dying with symptoms (prostration and subnormal temperature) indistinguishable from those of the untreated rat with its concentrated blood and reduced blood volume; and further injections serve only to increase the hydremia and perhaps precipitate death.

The duration of life shows no regular parallelism with the quantity of plasma injected. Furthermore, control experiments show that the injections used in average experiments of this type can be tolerated by normal adult rats without harm.

RESULTS OF INJECTIONS OF SALINE SOLUTION

Though the foregoing experiments were favorable to the assumption of a toxic factor, it seemed ·advisable to give further attention to one detail of the physical hypothesis. Notwithstanding all the published papers, it may be doubted whether there is any serious deficiency of proteins or other organic plasma constituents in the presence of shock. The current hypothesis might therefore be altered to the extent of assuming that the essential feature in shock is a need for fluid in the tissues rather than a lack of plasma in the blood. Under this assumption the plasma proteins might hinder the transudation of sufficient fluid; the binding of water would be increased as the proteins became more concentrated, and thus a plethora of plasma might be practically as detrimental as a plethora of corpuscles. The unfortunate experimental conditions precluded chemical analyses to determine the actual concentration of substances in the blood, but it was possible to compare the effects of injections of saline solution with those of injections of plasma. For this purpose either Ringer solution or a simple physiologic solution of 0.85 per cent sodium chloride in tap water was used. The results were not altered when heparin was added in the same quantities as used for the transfusions.

The reviving effect of injections of saline solution (merely warmed, not oxygenated) on rats at the point of death from shock was found to be practically nil. It was even less than the effect of plasma, and the rats commonly died either during the injection or very soon afterward. Therefore, the mere increase or dilution of the circulating fluid in this terminal stage of shock was of no practical benefit.

Other experiments were performed, after the preparatory high ligation of both hindlegs for five hours, with a series of injections of saline solution similar to the previous injections of blood and plasma. Within seven hours after release of the tourniquets, several intravenous injections were given in varying amounts, ranging from 5 cc. to a total of more than 20 cc. In other experiments injections of various amounts of saline solution were given subcutaneously or intraperitoneally, alone or combined with intravenous infusions.

The resulting curves approximately duplicate two forms of curve observed after injections of plasma, the red cell count remaining nearly uniform or rising moderately. The third form of result with plasma, namely the marked dilution of the blood (provided counts are not taken within a ridiculously short time after the injection) is practically unattainable with saline solution. Illustrating the well known ease with which saline solution leaves the blood vessels, in another experiment of this type a blood count was taken simultaneously with release of the tourniquet; half an hour later 6 cc. of saline solution was injected intravenously; half an hour after that a red cell count was taken and was

more than 2,000,000 higher than the first count. Here the avidity of the tissues for fluid was apparently such as to withdraw not only the 6 cc. of injected saline solution but also a considerable amount of plasma in this short time.

If there is abnormal permeability of the blood vessels in the presence of secondary shock, it must·be only in the direction of outflow. The rapid absorption of fluid which is familiar in dehydrated states is not evident in shock; and direct proof of delayed absorption was brought by Blalock [2b] for saline solution and by Daniel, Upchurch and Blalock [2c] for strychnine and phenosulfonphthalein. In the present experiments, injected saline solution remained for long periods in the peritoneum or subcutaneous tissue of animals with shock. Some quantitative idea was afforded by the fact that while an intravenous injection of 5 cc. of saline solution within three hours after release of the tourniquet has a marked influence on shock, subcutaneous or intraperitoneal injection of 5 or 10 cc. immediately after release has very little effect. With the same preparation, that is, five hours' ligation of both hindlegs, injections of 5 cc. of saline solution subcutaneously or intraperitoneally (or both) every three hours have failed to save life, though a few such injections intravenously have been effectual. In 1 extreme instance of this type, death occurred nine hours after release of the tourniquet. The original weight of the rat was 125 Gm.; the saline solution given in both subcutaneous and intraperitoneal injections amounted to 95 Gm.; the body weight of the animal at death was 205 Gm. This leaves only a possible 15 Gm. for loss through diuresis and respiration. The original red cell count at release was at a low level of 6,000,000; it rose steadily to 10,500,000 in three and one-half hours, remained approximately at this maximum for four and one-half hours, and fell slightly, so that for blood taken at autopsy it was 9,900,000. Here the large injections more than doubled the time of survival as compared with that observed for controls and probably limited the degree of concentration of the blood; but most of the fluid could be recovered from the peritoneum and subcutaneous space at autopsy, and death occurred with typical symptoms. In a few instances, the rats being presumably very strong, life was saved by large intraperitoneal and subcutaneous injections given early and repeated after some hours. In general, such injections are most useful as a convenient supplement to the intravenous injections. One or two small intravenous injections keep the animal alive long enough to allow time for the early subcutaneous or intraperitoneal injections to become effective, and thus the trouble of prolonged watching and repeated intravenous injections may be saved. It may also be assumed that this method involves less sudden and extreme fluctuations in concentration of the blood than must occur with large intravenous injections. Any other superiority of this method has not been

perceptible; also, a harmful effect of the intravenous injections in washing protein out of the vessels is not indicated by any symptoms.

The animals into which saline solution was injected as a group exhibited the greatest edema of all, owing partly at least to the longer period during which ligation was maintained. This edema, spreading beyond the ligated legs as usual, sometimes extended over the surface of the abdomen, halfway up to the axilla.

Injections of saline solution are effectual in proportion as they are given early after the release of the tourniquet. As has been mentioned, they are useless for an animal at the point of death. Injections at intermediate periods give intermediate results, sometimes saving life but more often prolonging it greatly without saving it. In a number of instances, when injections were begun two hours or more after the release or when they were begun promptly but in too small amount, it has been possible to keep the rat alive in a constantly weak condition until some time the next day by watching it all night and giving intravenous injections of saline solution every few hours, so that the red cell counts were kept approximately uniform. The most extreme example of this kind was presented by a strong young rat weighing 120 Gm. Ligation of both hindlegs was maintained for five hours. Owing to the fact that the ligatures slipped down a little, the animal at three and one-half hours after release was not in immediate danger, though too weak to turn over when placed on its back. The red blood cell count had risen from 8,000,000 to 11,500,000, and at this point treatment was begun with an intravenous injection of 5 cc. of saline solution. Strength was improved, and the erythrocyte count one hour later was found reduced to 9,750,000. By six repetitions of the same injection at suitable intervals this animal was kept alive for fifty-two hours from the time of release, while the red cell count was kept between 9,000,000 and 7,000,000 throughout this time. All such deaths may be explainable under the accepted doctrine that when the secondary constitutional changes produced by shock have reached a certain stage they progress fatally in spite of any treatment.

The most important result of these experiments was the discovery that early and adequate injections of saline solution afforded a means of regularly and permanently saving the lives of rats under conditions of otherwise hopeless shock. Without treatment, ligation of one hindleg for five hours was invariably fatal, but the injections saved life after ligation of two legs for five hours. In dozens of attempts with various methods, this result had not been accomplished in any instance by injections of blood or plasma. This result, while it demonstrated the importance of the physical factor of the simple shift of fluid even in this severe form of shock, also suggested that the most important condi-

tion is a need of the tissues for fluid. Apparently the investigators or surgeons who have complained that saline solution leaks out uselessly from the vessels have not given sufficient quantities to determine whether the final result is drowning of the organism or establishment of an equilibrium. The latter proves to be true, at least under the conditions of these experiments. The chief purpose of therapy, therefore, is to give not a fluid which will remain in the vessels but one which will pass readily out of the vessels. These experiments did not include tests of the permeability of vessels and therefore do not disprove the possible existence of abnormal permeability. But when saline solution is given from an early stage in sufficient amount to satisfy the avidity of the tissues, the supposed abnormal permeability of the vessels does not prevent the plasma from remaining in them without difficulty. These conditions are radically different from those of hemorrhage. Also there is no trouble from lack of proteins or other substances, and the body can evidently supply every element that is needed except water and probably sodium chloride. These findings are in accord with the empiric practice of most surgeons, who depend chiefly on large quantities of fluid for treatment of all conditions involving shock.

ACACIA

For comparison with the injections of plasma, a smaller number of experiments were performed with injections of acacia.[30] Whether made up with water or with physiologic solution of sodium chloride, the acacia solution gave results distinctly inferior to those with plasma and in some instances seemed definitely to hasten death, especially when large quantities were used. This experience harmonizes with the view (Walker and Keith,[31] MacFee and Baldridge [32]) that anything hindering egress of water from the vessels is harmful rather than helpful in cases of shock.

ABDOMINAL LIGATIONS

One of the aforementioned methods for increasing the severity of shock consists in extending the asphyxia over a larger area. This plan provides either an enlarged field of transudation or a greater mass of tissue to produce toxin, according to one or the other hypothesis.

Trials were therefore made with temporary occlusion of the abdominal aorta at various levels below the renal arteries. In such a small animal as the rat the result is accomplished better by a tourniquet around the unopened abdomen. If the rat, completely relaxed under ether, is held vertically with the head down, the viscera drop toward

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30. A 6 per cent solution of acacia was employed, prepared from the concentrated ampules acacia without sodium chloride of Eli Lilly & Co.

31. Walker, M. A., and Keith, N. M.: Am. J. Physiol. **95**:561-672, 1930.

32. MacFee, W. F., and Baldridge, R. R.: Ann. Surg. **100**:266-278, 1934.

the diaphragm so as to leave space for making several turns of a heavy rubber band around the lower part of the abdomen, stopping circulation completely.

The early effect of release of the ligature is a much more severe degree of shock than follows ligation of the hindlegs with a slighter degree of reactive hyperemia and edema of the ligated parts. The extreme limit of endurance is one and one-half hours; an exceptional rat may survive if the tourniquet has been placed very low, but the majority die within a few hours after release, with the typical rising curve of blood counts. Ligation for two hours has proved invariably fatal not only for untreated rats but for rats treated with transfusions of blood or plasma.

The later effects of nonlethal ligations of one-half hour or longer are: (1) paraplegia, clearing up within a few weeks; (2) paresis of the lower part of the bowel, usually only to the extent of transitory abnormality of defecation but sometimes fatal; and (3) retention of urine with dribbling, presumably due to prostatic swelling together with vesical paralysis. No attempt has been made to catheterize, and every male rat has died within nine days at most from hydronephrosis and presumably uremia. The method may therefore be of interest to persons desiring to produce such a condition experimentally. This difficulty was overcome by changing to female rats, which ordinarily recover after a few days of dribbling of urine. Also, the large size of the testes of adult male rats makes dangerous addition to the shock when ligations of long duration are used.

A series of female rats were subjected to such ligations for the fatal period of two hours. It was found possible to relieve the shock and obtain complete recovery by giving injections of saline solution, which checked the rising red cell counts in practically the same manner as with the ligation of the two hindlegs. Recovery occurred, that is to say, provided the intravenous injections were begun very early, alone or in combination with subcutaneous or intraperitoneal injections. The latter injections were never adequate without the intravenous injections. Also, the intravenous injections did not save life when started at a late stage, even though the corpuscle counts were reduced to normal.

These experiments showed that the compensation for displacement of fluid by means of injections of saline solution succeeds in controlling even shock resulting from asphyxia of extensive portions of the body. Under these conditions also, saline solution is superior to blood or plasma.

RESULTS WITH INTENSIFIED SHOCK

Abdominal ligations of the type described, continued for three or four hours, are invariably fatal regardless of any treatment, even though the measures employed may prevent increased blood counts.

Ligation of all four legs of a rat close against the body for five hours or longer was uniformly fatal in several trials. With this type of ligation also the blood count can be kept approximately normal by suitable injections of saline solution, but death occurs nevertheless.

For comparison, all four legs of a strong dog weighing 10 Kg. were ligated with heavy rubber bands for seven hours with the dog under amytal narcosis. Marked dyspnea began almost immediately after release and increased, with prostration, to death in one and one-half hours, while the red cell count rose by over 2,000,000. The legs of dogs and other large species do not flush and swell as rapidly as do those of rats after long ligations, and within the time mentioned the paws had scarcely become warm, and local edema was barely perceptible. It seemed obvious that the loss of plasma indicated by the blood counts must have occurred elsewhere than in the ligated parts. Also, considering the resistance of dogs to hemorrhage, it is scarcely conceivable that the precipitate symptoms and early death could have been due either to vascular dilatation or to migration of fluid in the ligated limbs.

With regard to the aforementioned examples of ligation of extensive masses of tissue it is possible to raise a question of nervous influence, gross circulatory disturbance, visceral injury (in the case of abdominal ligations) or other complication in addition to the pure shock. Clearer conditions may be obtained by making the injuries intensive rather than extensive. It is thus ascertained that the high ligation of one hindleg for eight to ten hours is inevitably fatal in spite of any treatment.

In such animals, the rise of the blood count can be controlled by the same amounts of injected saline solution which have been described as being life saving for animals with milder shock. At the same time, an adequate blood volume is indicated by the visible fulness of the superficial vessels and the easy flow of blood from the clipped tail. Larger injections of saline solution or supplements of any quantity of blood or plasma do not improve the results, even though carried to the point of distention of all visible vessels and engorgement of the heart. The difficulty is not in maintaining the desired volume and concentration of the blood but in the fact that the rats die in spite of treatment, with typical symptoms of shock. On the other hand, it may be recalled that after ligation of one or both hindlegs for even more than ten hours life can still be saved by sufficiently early amputation.

After a properly performed ligation maintained for such periods there is neither thrombosis nor gangrene, the limits of endurance of asphyxia by the local tissues being reached several hours later. Release of the tourniquet is followed by intense hyperemia and edema within a few minutes in the rat, and within a longer time in larger species. But as the period of survival after ligations of eight to ten hours' duration

is decidedly shorter than after ligations of four to five hours' duration, the resulting edema is less in the legs ligated for the longer period, and there is less extension to the adjoining parts of the body. This point came to notice too late in the present investigation to permit of making a statistical comparison of the weights of legs after long ligation with those subjected to shorter ligations in the earlier work, but the results of simple inspection seem sufficiently plain. The purely physical hypothesis, therefore, meets this obstacle, that the more severe and fulminant is the shock the slighter is the extent of local migration of fluids.

The factor of local vasodilatation may be discussed as follows: (1) It is not appreciably greater, according to gross observations, in a limb ligated for ten hours than in one ligated for five hours; (2) it has been .found to show its most powerful effect in reducing blood pressure soon after release of the ligature, whereas death occurs considerably later, and (3) it is inconceivable that this factor should be as great in an animal with one leg ligated for ten hours as in an animal with two legs ligated for five hours, yet the experiments show that the latter animal can be saved by injections of saline solution while the former cannot.

Therefore, unless persons more fortunately equipped, with facilities for continuous instead of intermittent injections, and for determinations of blood volume and blood chemistry and other direct data, are able to alter these facts or their interpretation, the only possible conclusion must be in favor of a toxic substance as the fundamental etiologic factor. Presumably the asphyxiated limbs will offer rich material for chemists seeking to identify this substance.

Although the symptoms become more severe and rapid as the time limit entailing tissue necrosis is reached and passed, they do not seem to differ in essential character from the results of ligations maintained for briefer periods, at least according to superficial appearances. It is therefore possible that no essential complication has been introduced in previous work, most of which has been done with shock of complicated causes, namely that produced by mechanical trauma, by burns or by freezing. With such injuries, clinical or experimental, at least three sources of disturbance are conceivable, aside from a nervous factor; first, the absorbed products from dead tissues or blood clot; second, the products of tissues damaged but not killed, and third, the physical factor of fluid migration, represented by edema in the adjoining parts. The possibility is open that the shock-producing substance derived from asphyxiated, traumatized, dying or dead tissues is one and the same, or that there is a series of related substances having similar effects. The accurately controllable gradations of local asphyxia offer a means of deciding such questions.

An additional argument may perhaps be furnished by more detailed study of an observation which was made only cursorily; namely, application of a loose tourniquet (so as to produce suitable obstruction of veins without cutting off the arterial inflow) results in edema which apparently may be greater than that which follows tight ligation, and yet the rats survive the loose ligation for six to twelve hours with little or no sign of shock.

THERMAL INFLUENCES DURING LIGATION

The following are a few pertinent facts taken from another phase of the investigation, to be published elsewhere: Elevations of temperature of various grades up to +1 C. increase the effects of ligation and shorten the time for which it can be endured. Oppositely, reductions of temperature diminish the effects. Thus, when the ligated parts are refrigerated by being kept immersed in ice water, the otherwise surely fatal ligations of the hindlegs for eight hours and of the abdomen for three hours can be carried out safely; the changes in the blood are minimized, and recovery is readily obtained. While it is evident that hyperemia and edema are augmented by heat and reduced or retarded by cold, the facts previously stated turn one's attention predominantly to metabolism in the tissues. It appears most probable that the metabolic processes which give rise to the shock toxins in asphyxiated tissue are accelerated by heat and inhibited by cold. These experiments also reproduce all the mechanical disturbances, together with the subsequent paralyses and visceral damage, described for the most extensive ligation experiments, and they therefore prove that these disturbances are not responsible for the fatal results. Furthermore, the special mode of confinement and the methods necessary for guarding against fall of the body temperature entail greater general strain on the organism than does simple ligation.

OTHER THERAPEUTIC ATTEMPTS

Orientation experiments were performed with several methods other than injection of fluids, partly for comparison with the known results in other forms of shock and partly for light which they might throw on the nature of the condition.

· The fall of rectal temperature, often below 30 C., is more marked in rats than in larger animals. This fall occurs when rats are allowed to suit their own comfort, usually by huddling among other rats in a cage. Chilling accentuates the fall of temperature and apparently hastens death slightly, as is supposed to be true of the human being. Attempts to keep the temperature normal or to raise it after it has fallen by placing the animal on a heated surface or in a warm air chamber or a warm bath produce signs of discomfort in the animal and decidedly hasten death.

Injections of various doses of dinitrophenol were also given, with a view to raising temperature by increasing oxidation in the protoplasm. Doses large enough to have any perceptible effect hastened death.

On account of the dyspnea and especially because of the very dark blood in later stages, oxygen was administered, without success.

Dextrose was tried subcutaneously and intravenously, because of its status as a food and as a cardiac stimulant, and also because of the recommendations for its use in human shock by several authors (cf. also Mazzola and Torrey [33]). The artificial hyperglycemia thus produced seems to be not only useless but distinctly harmful in this form of secondary shock in rats.

Results of a few attempts with sodium bicarbonate, suggested by the dyspnea and also by the possibility of the presence of acid products derived from the asphyxiated tissues, were not encouraging.

Injections of hypertonic saline solution, made with a view either to restoring circulatory electrolytes (Gilman,[34] Doménech-Alsina [35]) or as a possible relief for central nervous edema which might be responsible for the terminal apnea, likewise failed to improve results.

Crude trials of epinephrine hydrochloride were without benefit. Also, though stress has been laid on the suggestive resemblance between secondary shock and deficiency of the adrenal cortex (Swingle and his collaborators; [36] Heuer and Andrus; [37] criticism by Freeman [38]), a commercial preparation (eschatin), given in the attempt to save rats which had reached the late, fatal stage of shock, seemed useless in small doses and probably harmful in large doses. (I found it also unavailing for a diabetic patient in the terminal stage of coma.)

Attempts to produce either habituation or immunity to the supposed toxin, by subjecting rats to repeated ligations of various amounts of tissue at various intervals during a number of weeks, definitely failed to make them more resistant than untreated rats.

In a series of rats which had undergone ligation of legs for sufficient periods to assure fatal degrees of shock, a variety of attempts were made with subsequent refrigeration of the limbs (preserving warmth of the body) for the purpose of retarding the hyperemia and edema or the absorption of toxic material in the asphyxiated tissues,

33. Mazzola, V. P., and Torrey, M. A.: Am. J. Obst. & Gynec. **25**:643-653, 1933.

34. Gilman, A.: Am. J. Physiol. **108**:662-669, 1934.

35. Doménech-Alsina, F.: Rev. de cir. de Barcelona **4**:369-383, 1932.

36. Swingle, W. W.; Pfiffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: Science **77**:58-64, 1933. Swingle, W. W., and Parkins, W. M.: Am. J. Physiol. **111**:426-439, 1935. Parkins, W. M.; Taylor, A. R., and Swingle, W. W.: ibid. **112**:581-590, 1935.

37. Heuer, G. J., and Andrus, W. D.: Ann. Surg. **100**:734-741, 1934.

38. Freeman, N. E.: Science **77**:211-212, 1933; Ann. Surg. **101**:484-493, 1935.

with the hope that a more gradual onset of shock might favor the resistance and survival of the animal either spontaneously or with the aid of transfusions or saline injections. No encouragement was gained in this direction.

Also, in the later stages of shock, whether or not the animals had been given transfusions or injections of saline solution, all four legs were ligated close against the body in order to cut off the most distant vascular tracts in which stagnation may most readily occur and to allow all the circulatory, nervous and hormonal resources to be concentrated in the trunk and head, in an effort to save life at sacrifice of the limbs. This also proved harmful rather than helpful.

The conclusion may be quoted in the words of Mann and Essex:[39] "When the tissues of the body have been subjected to an inadequate flow of blood for too long a period of time, no treatment yet devised will save life."

<div style="text-align:center">COMMENT</div>

It is possible to distinguish theoretically three entities included in the present interpretation of the word shock. One of these is the neural injury, which may partly be defined as to anatomic lesions and physiologic effects, such as reduction of blood pressure, and may appropriately be covered by the term shock, because of its vagueness and because of the logical relation to the original meaning of the word.

The second is the other element which is often assumed to exist in primary shock, namely, an influence of the injured tissues apart from the nervous injury. Neither the nature nor the actual existence of this element has been positively demonstrated, but it should be subject to investigation in tissues separated from their nerve connections, and the part played by circulatory factors, dehydration, temperature, infection, tissue toxins or anything else should be definable.

The third is the condition now called secondary shock; and since this is recognized as being entirely different from primary shock and also is a departure from the everyday meaning of the word shock, a replacement of this clumsy designation by something more definite seems desirable. While the evidence obtained in the present investigation is unfortunately only indirect, it at least suggests some such provisional name as histotoxicosis. The vasomotor and other phenomena may thus be conceived as resulting from nervous and humoral agencies, which supplement each other as in so many other physiologic processes. This hypothesis at least offers a rational explanation of the entire range of events, classifiable in three degrees: (1) injury such as a small contusion or burn, in which the combined nervous vasodilatation and histotoxin production cause only local redness and swelling without

39. Mann, F. C., and Essex, H. E.: Am. J. Surg. 28:160-165, 1935.

appreciable constitutional effects; (2) more extensive damage, involving primary general vasomotor disturbances of nervous origin and the formation of greater quantities of histotoxin, which not only augment local transudation but also escape into the circulation and set up similar processes throughout the body (this loss of fluid, however, can still be compensated for by administration of sufficient fluid); (3) still more extensive or intensive damage, in which either the primary nervous disturbance or the secondary production of histotoxin may be fatal in spite of preservation of the fluid balance at all stages.

The final demonstration and designation must be left to the chemist, who may be able to identify the hypothetic histotoxin. Local asphyxia may be regarded as the ideal method for this study, because of the simple and accurate control, exclusion of the nervous factor by the ligation, absence of dead or dying protoplasm, avoidance of other complications and possibility of full recovery of the animals when desired. There may even be conjecture whether the condition of secondary shock, or histotoxicosis, uniformly originates from asphyxia, in the sense that injuries may disturb cell respiration. Regardless of this speculation, the proved fact that this condition can be caused by tissue asphyxia supports the opinion that a variety of conditions, including infection, intoxication, hemorrhage, dehydration, circulatory or respiratory failure or any prostration severe enough to cause a certain deficiency of blood supply in any part or throughout the body, may give rise to asphyxial histotoxicosis, and that the clinical difficulty of distinguishing these states sharply from the so-called secondary shock may be due to an essential and inevitable mingling of the conditions.

SUMMARY AND CONCLUSIONS

1. As former authors have shown, the most distinctive characteristic of secondary shock is the increased concentration and reduced volume of the blood, caused by migration of fluid into the tissues, and the changes in red cell content are the most quickly and easily ascertained index of this process. Temporary local asphyxia of limbs or other tissue masses appears to offer the best experimental means for producing this condition, because of its simplicity, its accuracy of control, its freedom from complication by tissue necrosis and other conditions and the opportunity it affords for studying various details.

2. Traumas which typically produce primary shock, repeated during a period equal to that within which secondary shock is able to manifest itself, fail to cause the characteristic blood changes of secondary shock, thus corroborating the view that the two conditions are radically different. Circumstances did not permit of determining whether any other primary effect can arise from mutilated tissues, for example, after denervation.

3. The effects of local asphyxia, as regards both changes in the blood and the attendant symptoms and death of the animals, can be prevented by sufficiently early amputation of the asphyxiated parts, as is already known of similar operations on the human being. Amputation does not save life at a later stage, after more advanced changes in the blood have occurred.

4. The following therapeutic observations have been made with various methods of replacement of the migrated fluid:

(*a*) Animals at the point of death may be strikingly revived by transfusions of whole blood, while separated corpuscles or plasma have less value and saline solution has practically none. Such recovery is always brief, and no amount of the fluids mentioned actually saves life at this stage.

(*b*) Death, which regularly occurs under certain standard conditions, e. g., after five or six hour asphyxia of one hindleg of a rat, is preventable by early transfusions with blood or plasma, not with corpuscles. These results, and those under *a*, agree fully with the clinical evidence of the value of transfusions of blood or plasma to compensate for loss of circulating fluid under certain conditions in shock. An equivalent benefit by acacia solution [40] was not demonstrable.

(*c*) The results mentioned under *a* and *b* are obtained practically as well with the blood of animals dying in shock as with normal blood. This disproves the existence of any considerable amount of toxin in the circulation.

(*d*) After asphyxia of extensive masses of tissue, transfusions of blood or plasma no longer suffice to save life, even though the corpuscle count is kept at a normal or reduced level and all indications point to normal or increased blood volume together with adequate propulsion of the blood. Theories which regard these as the determining factors in shock are thus invalidated.

(*e*) In the conditions described under *d*, simple injections of saline solution are able to save life when plasma fails. It is deduced that the essential physical factor is the obligatory edema or avidity of the tissues for fluid, and that the most important requisite in treatment is a fluid which will pass easily out of the vessels to satisfy this need. When this is supplied, the plasma automatically remains in the vessels. The composition of the blood and the animal's life are preserved, notwithstanding abnormal permeability of the vessels or other supposed changes.

(*f*) After more intensive, i. e., more prolonged asphyxial injury of tissues, death occurs in spite of injections of saline solution which

40. Stanbury, J. B.; Warweg, E., and Amberson, W. R.: Am. J. Physiol. **107**: 230-236, 1936.

prevent rise of the corpuscle count and maintain the gross appearances of adequate filling and circulation in the vessels. It seems possible that the composition of either the blood or the tissues is altered to fatal degree.

(*g*) Various therapeutic attempts along other lines than fluid replenishment have failed, so that the physical hypothesis must be credited with suggesting the only helpful form of treatment.

5. The effects of local asphyxia, as regards changes in the blood, symptoms and death, are augmented by heat and inhibited by refrigeration of the parts during asphyxia.

6. On the basis of the evidence in favor of the toxic *hypothesis*, it is suggested that a substance or substances derived from the injured protoplasm may be a highly important factor affecting the vascular permeability, edema formation and other symptoms. The usefulness of such a term as histotoxicosis is therefore provisionally suggested.

KRUKENBERG TUMOR

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In 1896 Frederick von Krukenberg described a rare type of ovarian tumor of which he had seen 5 instances. The tumor presented certain characteristics of form and growth not seen in other ovarian tumors. It affected both ovaries and was solid; it was actually accompanied by ascites and was free from adhesions. Histologically it had a fibrosarcomatous-appearing stroma which enclosed large cells with a mucoid-like protoplasm. Often these cells had a nucleus displaced to the periphery. which gave them a "signet ring" appearance. Von Krukenberg believed the tumor to be a form of sarcoma and christened it "fibrosarcoma ovarii mucocellulare." The comparative rarity of the Krukenberg tumor is shown by the scant number which have been reported in the medical literature. Masson [1] in 1934 reported 5 cases observed at the Mayo Clinic from 1909, although he stated that in earlier files there are records of other tumors which might have been Krukenberg tumors. By 1918 Major [2] was able to collect reports of 54 cases, to which he added the report of a case of his own. In 1929 Fallas [3] reported 23 additional cases, including 2 of his own. In 1930 Hundley [4] brought the number to 102, and since then, up until 1934, 3 cases have been reported in American literature and 10 in foreign journals. The foregoing summary is taken from the work of Andrews,[5] who with 3 cases of his own brought the total number of reported cases to 118 in 1934. Since then. several cases have been reported both in this country and abroad.[6]

From the service of Dr. E. MacD. Stanton and Dr. Charles W. Woodall, Ellis Hospital.

1. Masson, J. C.: Krukenberg Tumors of the Ovary, Am. J. Obst. & Gynec. 27:825, 1934.

2. Major, R. H.: A Study of the Krukenberg Tumor, Surg., Gynec. & Obst. 27:195, 1918.

3. Fallas, R.: Krukenberg Tumor of the Ovary with Report of Two Cases, Surg., Gynec. & Obst. 49:638, 1929.

4. Hundley, J. M., Jr.: Krukenberg Tumors and Other Secondary Ovarian Carcinomas, South. M. J. 24:579, 1931.

5. Andrews, C. J.: Krukenberg Tumor of the Ovary, South. M. J. 27:597, 1934.

6. Armstrong, M. V., and Wolfe, S. A.: Krukenberg Tumor of the Ovary. Am. J. Obst. & Gynec. 27:906, 1934. Horsley, J. S., Jr.: Krukenberg Tumor of the Ovary, South. Med. & Surg. 96:272, 1934. Runyeon, F. G.: The Krukenberg Tumor, J. A. M. A. 103:1199 (Oct. 20) 1934. Comando, H. N.: Krukenberg Tumor of the Ovary, Am. J. Surg. 26:575, 1934. Fennel, E. A.: Krukenberg Tumor, ibid. 30:376, 1935.

Although at the time of this writing the total number of reported cases still remains well under 150, there is fairly voluminous literature on the subject. Of particular interest in this literature is the question of pathogenesis. It is generally conceded that the ovarian tumor is a secondary or metastatic growth, the primary lesion of which occurs most frequently in the stomach but occasionally in the intestines or in the gallbladder. It is entirely possible that the few tumors which were thought to be primary growths in the ovaries would have turned out to be secondary had a careful enough search been made at postmortem examination. This possibility is illustrated in the case reported by Major,[2] who discovered the primary growth only after studying serial sections of the stomach. In most cases in which autopsy has been done, observations have shown the primary growth to have been elsewhere than in the ovaries. Jarcho[7] reported 7 cases of Krukenberg tumor; 6 of the lesions were proved at autopsy to have arisen from a primary growth in the stomach. In the seventh case autopsy was not performed.

The mode of metastasis from the stomach or intestines to the ovaries opens up an interesting field of speculation. At least three theories have been suggested, as follows:

1. Implantation from malignant cells cast loose from the parent growth, which have floated through the abdomen and become attached to the ovaries. This theory can be dismissed without too much credence because of the medullary nature of the ovarian growth. The serous capsule is not involved except by extension from within.

2. Extension through the blood stream. One does not ordinarily think of carcinoma metastasizing through the blood stream, but there are certain features about Krukenberg tumors with other associated metastases which justify some belief in the hematogenous theory. Jarcho[8] in a recent publication has shown most interestingly the close relation between lymphangitic carcinomatosis of the lungs, metastatic infiltration of carcinoma in bone marrow and Krukenberg tumors, all of which arise most often as secondary manifestations of a flat, infiltrating scirrhous carcinoma of the stomach. He pointed out that the metastases to the lungs can be accounted for by retrograde dissemination along the lymphatics from the hilus toward the pleura, but that actually tumor cells are occasionally found in the blood vessels of the lungs as well as in the lymphatics. This could be accounted for by the passing of tumor cells from the thoracic duct into the blood stream. As regards the bone marrow, hematogenous metastasis seems to be the only explanation, as up to the present time no lymphatics have ever been demonstrated in bone marrow.

7. Jarcho, J.: Krukenberg Tumors and Their Practical Problems, Am. J. Obst. & Gynec. **13**:288, 1927.

8. Jarcho, S.: Diffusely Infiltrative Carcinoma, Arch. Path. **22**:674 (Nov.) 1936.

3. Retrograde metastasis along the lymphatics. This is the theory which seems to have the widest support. It suggests that there has been an early blocking of the lymphatic reservoir. The frequent association of ascites with Krukenberg tumors would be explained by this theory.

In the light of the recent work reported by Jarcho [8] it seems questionable that the Krukenberg tumor is a separate entity. It seems, rather, to be one expression of diffusely infiltrative carcinoma occurring in women, in whom the predominant metastases are in the ovaries.

REPORT OF A CASE

The following case is one of a Krukenberg tumor of the ovary with primary growth in the stomach, as proved by autopsy.

History.—Mrs. R. D., an Italian woman aged 30, came to my office on Jan. 16, 1937, complaining of backache and of pains in the pelvis. There was no definite date of onset, but there had been a gradual increase of painful symptoms. She had no urinary trouble. The menstrual function was somewhat irregular; menstruation would occur at intervals of anywhere between twenty and thirty days. The bowel movements were irregular. There was a moderate vaginal discharge. At times, bending would cause severe abdominal pain and nausea. The past history was not notable. The patient had had three children, the youngest being 5 years of age. She had had no miscarriages.

Examination.—Physical examination showed a well developed woman of excellent color. The head and neck were normal. The heart and lungs were normal; no audible rales were found. The pulse rate was 100; the temperature was 99.6 F. The abdomen was somewhat distended; generalized tenderness was present over the lower half. The patient was very obese, and a considerable amount of free fluid was present in the abdomen, so that abdominal palpation and bimanual pelvic examination were not particularly enlightening. However, there was marked resistance in the lower part of the pelvis, and it was thought that some mass could be felt in the right fornix. Urinary examination showed a specific gravity of 1.028, with no albumin or sugar; microscopic examination showed nothing pathogenic. The patient was sent to the Ellis Hospital with a tentative diagnosis of an inflammatory condition of the pelvis, based on the tenderness in the pelvis accompanied by moderate fever and on a history of five years' sterility. As she was first seen on a Saturday afternoon and had no acute symptoms indicating immediate operation, a laparotomy was scheduled for the following Monday morning. Early on Monday morning she noticed an acute pain in the pelvis. She was brought to the operating room at 8:30. Before operating, I noticed that there was considerable increase in the size of the abdomen, apparently caused by the volume of free fluid.

Operation.—The operation was performed with the patient under cyclopropane anesthesia. A low median incision was made. When the peritoneum was opened several quarts of straw-colored free fluid escaped, and a solid tumor of the right ovary presented itself. It was somewhat hemorrhagic in appearance and was edematous, with dark purplish areas on the peritoneal surface. The tumor was free from adhesions and was completely twisted on its pedicle, through 365 degrees.

The tumor was approximately 6 inches (15 cm.) in diameter. The left ovary, while slightly enlarged, did not present any definite gross abnormality. After the intestine had been packed back, numerous flat, grayish patches scattered along the course of the lower part of the sigmoid flexure of the colon and the upper part of the rectum were observed. No similar patches were noticed through the lower part of the abdomen. Palpation of the upper part of the abdomen did not reveal any nodules on the surface of the liver, in the stomach or in other neighboring structures. The right ovary was excised. In addition, both tubes were removed to prevent possible pregnancy in a patient who obviously was suffering from a carcinoma of the ovary with metastases. The whole operation consumed thirty-five minutes, and the patient's condition was excellent both during the operation

Fig. 1.—Photograph of the cut surface of the right ovary (reduced).

and at its close. The highest pulse rate was 96. During the day of the operation (January 18) and on the morning of January 19 her condition was entirely satisfactory. The highest temperature on the evening of the operation was 99.6 F., and the highest pulse rate 92. The next morning the temperature was 98 F. and the pulse rate 86. During that night, however, something happened to induce a fever, and the next morning the temperature was 102.6 F. and the pulse rate 100. By night the temperature was 104.4 F. and the pulse rate 126. From that time on there was a steady but gradual rise in pulse rate and temperature until the time of her death on January 25, when the terminal temperature reached 108 F. and the pulse became uncountable. During all this time the respiratory rate remained below 30, and there was no evidence of pulmonary involvement. There was some gaseous distention of the abdomen accompanied

by dilatation of the stomach and occasional vomiting. This was fairly well controlled by the use of gastric lavage and the Levine tube. Hypodermoclysis several times as well as proctoclysis supplied the patient with body fluids. During all this time there was no evidence of intestinal obstruction, nor did I believe that there was any real peritonitis, as the abdomen, despite some distention, was soft and not tender. The patient died at 1:30 a. m. on January 25.

Pathologic Report.—The pathologic report on the operative specimens showed the right ovary to be a flattened oval mass 15 by 11 by 6 cm., weighing 625 Gm. The entire serosa was smooth except for a small area to which the pedicle was attached. Numerous yellowish nodules were seen under the serosa, but none penetrated it. Many hemorrhagic and mucinous foci were also seen. The tubes showed acute inflammation in an early stage. A diagnosis of metastatic car-
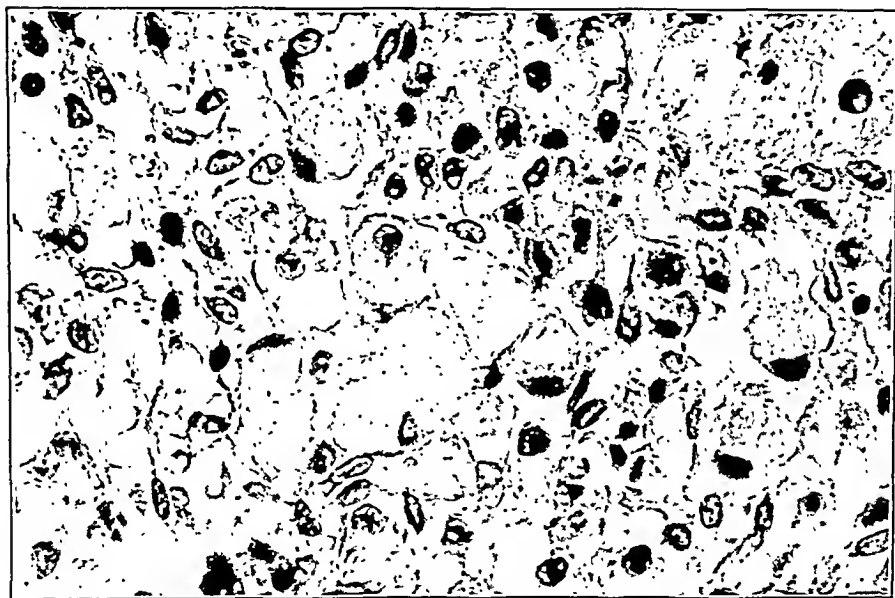
Fig. 2.—Photomicrograph of a section of ovary, showing characteristic "signet-ring" cells; × 80.

cinoma, so-called Krukenberg tumor, was made. Fortunately permission for autopsy was granted. The following pathologic report is a condensation of the report of Dr. Korkosz, assistant pathologist at the Ellis Hospital:

Examination of the peritoneum disclosed about 300 cc. of turbid yellow fluid in the cul-de-sac and right gutter. The peritoneum overlying the rectum was markedly injected and dull. The remainder, however, was of normal color and luster except that of the right half of the diaphragm, which was covered by numerous flecks of fibrin. No adhesions were present. The appendix appeared normal. The mesenteric nodes were palpable.

No fluid was present in either pleural cavity. A single dense fibrous band was separated with difficulty in the midportion of the left lung laterally.

The lower half of the left lung was markedly congested. The cut surfaces were dark red. The entire lung exuded considerable pink thin frothy fluid.

Slight crepitus was elicited over the upper half of the lung. The right lung resembled the left.

The pericardial sac contained about 20 cc. of clear yellow fluid. The pericardium appeared normal.

The heart, spleen, pancreas and gallbladder were normal.

The liver was not enlarged; it was pale brown, and its surfaces were smooth. Two white nodules 0.5 cm. in diameter were present on the convex surface of the right lobe. Their cut surfaces were grayish white and smooth. They were sharply delimited from the liver tissue. The cut surfaces of the liver throughout were slightly paler than normal. The lobules were distinct and appeared congested. There was no evidence of neoplasm within the liver.
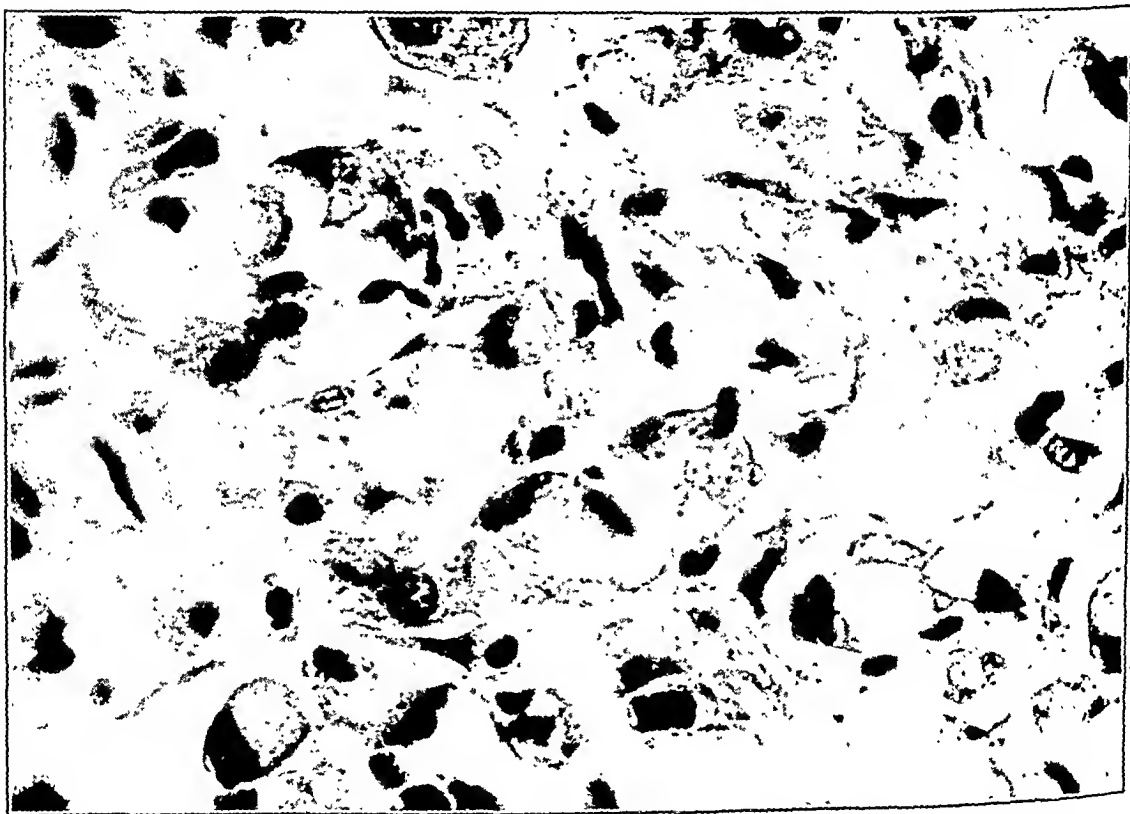
Fig. 3.—Photomicrograph of a section of ovary showing Krukenberg tumor; × 400. The primary lesion was in the stomach.

The stomach was markedly dilated with gas. It also contained about 200 cc. of foul-smelling brown fluid. The mucosa showed occasional small hemorrhagic foci. An oval ulcer 2 by 1 cm. was seen on the greater curvature, near the fundus. (This ulcer was on the posterior wall of the stomach and was not palpable; it was not found until the stomach was removed and opened [C. W. W.]). The edges were firm and slightly elevated. The floor of the ulcer was smooth; the serosa opposite the ulcer appeared normal. The small intestine was moderately distended. The large intestine was markedly distended with gas. The serosa overlying the rectum and a portion of the sigmoid flexure showed many firm, flat yellow plaques. The mesosigmoid contained many firm nodules which averaged 1 cm. in diameter and the cut surfaces of which were smooth and gray. None of the nodules were sharply outlined. Many similar nodules were found

Fig. 4.—Photomicrograph of a section of gastric carcinoma; × 150. Note the infiltrated mucosa and the deep lying tumor acini. Metastases to the ovaries occurred.

Fig. 5.—Photomicrograph of a section of gastric carcinoma; × 300. Note the tumor acini invading the muscle coat.

in the mesentery. The largest was about 2 cm. in diameter and was found adjacent to the greater curvature of the stomach, near the ulcer which has been mentioned. It was fairly well delimited from the surrounding fatty tissues. The mucosa of the large and small intestine showed nothing of note.

The adrenal glands, the kidneys and the uterus were normal.

The left ovary measured 6 by 3.5 by 3 cm. Several firm nodules were palpable. On section, these were grayish white, with smooth surfaces. Several follicular cysts and corpora lutea were also present.

The anatomic diagnosis was as follows: carcinoma of the fundus of the stomach; metastatic carcinoma of the ovaries, the intestine, the omentum, the liver, the lung and the diaphragm; early acute pelvic peritonitis; acute sub-diaphragmatic inflammation (?); edema of the lungs, and acute dilatation of the stomach and intestine. (What was thought to be acute subdiaphragmatic inflammation was later found to be a layer of connective tissue embedded with neoplastic cells and not an inflamed process due to infection.)

Bacteriologic Study.—A smear of the peritoneal fluid showed a few large round mononuclear and occasional polymorphonuclear leukocytes, occasional erythrocytes, rare gram-positive cocci found in pairs and short chains and rare gram-negative bacilli. A culture of the fluid yielded Bacillus coli and Staphylococcus albus. A culture of the blood in dextrose broth yielded B. coli.

Microscopic Examination.—The alveoli contained many red blood cells, lymphocytes and some large mononuclear cells. Many mononuclear cells contained coarse black granules. The capillaries were congested. Several perivascular lymphatics contained clumps of polygonal cells in which were many atypical mitotic figures.

The nodules described as being on the convex surface of the right lobe of the liver consisted of well defined foci of cells arranged in acini embedded in connective tissue. Slight lymphocytic infiltration was present. The nodule was not encapsulated. Direct invasion among the liver cells was seen. In some places partial destruction of the liver cells was demonstrable. The remainder of the section showed the liver cells to contain many droplets of fat, some of them presenting a "signet-ring" appearance.

That portion of the mucosa of the stomach taken from the elevated margin about the ulcer showed the cells to be extremely variable in size and shape. The staining of the cytoplasm varied in the different cells from red to blue. Great numbers of atypical mitotic figures were seen. Some of the cells were distended with mucin and presented the "signet-ring" appearance. The cells were arranged singly, in strands and in acini, many of which were deformed. Marked invasion of the muscularis was present. Many lymphatics were dilated by clumps of neoplastic cells. Great numbers of the smaller lymphatics contained single tumor cells. Scattered foci of lymphocytes were seen. The floor of the ulcer showed pink granular detritus, scattered neoplastic cells and lymphocytes.

The peritoneal surface had a layer of connective tissue in which were embedded neoplastic cells similar to those seen in the stomach. There was no penetration into the muscles of the diaphragm, but on the upper surface were many tumor cells.

Great numbers of neoplastic cells were present in the fatty tissue of the omentum, forming nodular masses.

There was diffuse infiltration by single large round and oval cells with clear cytoplasm displacing the nucleus to one side. Occasional mitotic figures were seen. There was no tendency to the formation of acini or strands of cells as seen elsewhere.
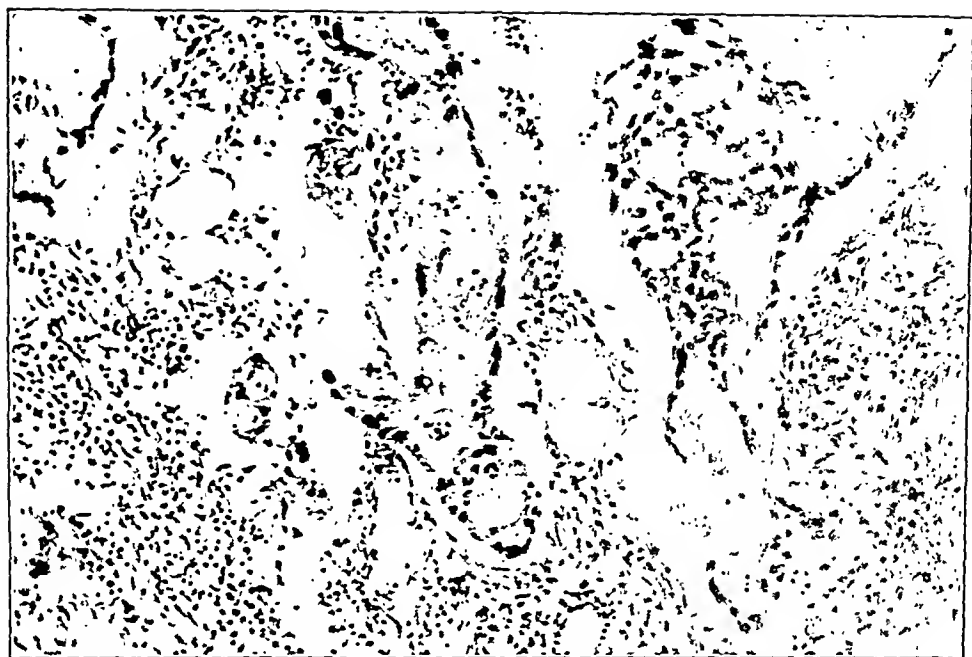
Fig. 6.—Photomicrograph of a section of omentum, showing infiltration by tumor; × 300.

Fig. 7.—Photomicrograph of a section of pulmonary tissue showing tumor cells in the perivascular lymphatics; × 300.

The following is a comment on the autopsy by Dr Kellert, chief pathologist of the Ellis Hospital:

Death in this case may be attributed to widely disseminated carcinosis, arising primarily in a small carcinoma of the stomach. Early extension to the ovaries resulted in bilateral carcinoma of those structures, which exhibited the histologic appearance of a typical Krukenberg tumor, which is generally conceded to take orgin in the gastrointestinal tract or accessory organs.

I do not feel that the observations made at autopsy satisfactorily explained the postoperative death in this case any more than those made clinically. From a clinical standpoint, the temperature curve ending in the excessively high temperature of 108 F. was certainly not accounted for by any infection which was discovered. The appearance of the abdomen at autopsy was not that of peritonitis, there being only a slight amount of peritoneal reaction in the pelvis, which might be expected after a laparotomy. The bacteriologic culture of abdominal fluid yielding B. coli is no more than might be expected from postmortem contamination. The rare gram-positive cocci and the rare gram-negative bacilli found in the smears of peritoneal fluid were not, I believe, pathologically significant. It is unfortunate that an autopsy of the brain was not performed, as it is possible that that might have thrown some light on the postoperative picture.

THE BLOOD IN THROMBOANGIITIS OBLITERANS

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AND

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Although thromboangiitis obliterans is considered a local vascular disease, its progressive course and the occasional general distribution of its lesions suggest a systemic origin. Increasing numbers of autopsy and clinical reports [1] indicate that almost any artery of the body may be the site of thrombosis. Bacteriologic studies [2] have not established

1. Telford, E. D., and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. 1:863-866 (April 27) 1935. Averbuck, S. H., and Silbert, S.: Thrombo-Angiitis Obliterans: The Cause of Death, Arch. Int. Med. 54:436-465 (Sept.) 1934. Allen, E. V., and Willius, F. A.: Disease of the Coronary Arteries Associated with Thrombo-Angiitis Obliterans of the Extremities, Ann. Int. Med. 3:35-39 (July) 1929. Perla, D.: An Analysis of Forty-One Cases of Thrombo-Angiitis Obliterans, with a Report of a Case Involving the Coronaries and the Aorta, Surg., Gynec. & Obst. 41:21-30 (July) 1925. Birnbaum, W.; Prinzmetal, M., and Connor, C. L.: Generalized Thrombo-Angiitis Obliterans: Report of a Case with Involvement of the Retinal Vessels and Suprarenal Infarction, Arch. Int. Med. 53:410-422 (March) 1934. Jäger, E.: The Pathologic Anatomy of Thrombo-Angiitis Obliterans in Juvenile Gangrene of the Extremities, Virchows Arch. f. path. Anat. 284:526-583 (May) 1932. Taube, N.: Mesenteric Involvement in Buerger's Disease, J. A. M. A. 96:1469-1472 (May 2) 1931. Barron, M. E., and Lilienthal, H.: Thrombo-Angiitis Obliterans: General Distribution of the Disease. Arch. Surg. 19:735-751 (Oct.) 1929. Brown, G. E.: Thrombo-Angiitis Obliterans, Surg., Gynec. & Obst. 58:297-309 (Feb. 15) 1934. Buerger, L.: Vasomotor and Trophic Disturbances of the Upper Extremities, Am. J. M. Sc. 149:210-229, 1915

2. Buerger, L.: Thrombo-Angiitis Obliterans: Experimental Reproduction of the Lesions, Arch. Path. 7:381-390 (March) 1929. Horton, B. T., and Dorsey, A. H. E.: Experimental Thrombo-Angiitis Obliterans: Bacteriologic and Pathologic Studies, ibid. 13:910-925 (June) 1932. Rabinowitz, H. M.: Experiments on the Infectious Origin of Thrombo-Angiitis Obliterans and the Isolation of a Specific Organism from the Blood Stream, Surg., Gynec. & Obst. 37:353-360 (Sept.) 1923.

infection as the cause of thrombosis, and neither infection nor thrombosis adequately explains the clinical and pathologic peculiarities of the disease. Homans [3] expressed the belief that the inflammatory characteristics [4] of the peripheral lesions are secondary changes due to thrombosis and to complicating infection. The lack of knowledge concerning thromboangiitis obliterans has made early diagnosis difficult and evaluation of therapeutic measures uncertain.

Changes in the circulating blood in thromboangiitis obliterans, as reported by Koga [5] in 1913, led him to believe that the vascular disease is secondary to increased viscosity of the blood. Accordingly, the treatment he recommended was directed to diluting the blood. Since then, many modifications [6] of his treatment seem to demonstrate the beneficial clinical effect accompanying a reduction in viscosity. More recent investigators [7] report various changes of the blood in thromboangiitis obliterans, either as a cause or as an effect of the disease.

3. Homans, J.: Thrombo-Angiitis Obliterans, in A Textbook of Surgery, Springfield, Ill., Charles C. Thomas, Publisher, 1931.

4. Buerger, L.: Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924; Pathology of Thrombo-Angiitis Obliterans, M. Rec. **97**:431-437 (March 13) 1920; Thrombo-Angiitis Obliterans, in Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1929, vol. 3, p. 755.

5. Koga, G.: Treatment of Spontaneous Gangrene of the Extremities, Deutsche Ztschr. f. Chir. **121**:371-382 (Feb.) 1913.

6. (*a*) McArthur, L. L.: Thrombo-Angiitis Obliterans of Buerger: Modified Koga Treatment, S. Clin., Chicago **1**:499-503 (June) 1917. (*b*) Meyer, W.: Conservative Treatment of Gangrene of the Extremities Due to Thrombo-Angiitis Obliterans, Ann. Surg. **63**:280-296 (March) 1916. (*c*) Steele, W. A.: Sodium Citrate Treatment in Thrombo-Angiitis Obliterans, J. A. M. A. **76**:429-431 (Feb. 12) 1921. (*d*) Ravinia, A., and Trosier, J.: Obliterative Endarteritis Gangrene Treated by Intravenous Injection of Sodium Citrate, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:670-682, 1924. (*e*) Silbert, S.: Treatment of Thrombo-Angiitis Obliterans, J. A. M. A. **86**:1759-1761 (June 5) 1926; Thrombo-Angiitis Obliterans: Results of Treatment with Hypertonic Salt Solution, ibid. **94**:1730-1733 (May 31) 1930; Thrombo-Angiitis Obliterans, Surg., Gynec. & Obst. **61**:214-222 (Aug.) 1935. (*f*) Rabinowitz, H. M.: The Use of Sodium Iodide Thiosulphate in the Treatment of Thrombo-Angiitis Obliterans, J. Chem. **13**:1-4 (April) 1936.

7. (*a*) Rabinowitz, H. M.: Thrombo-Angiitis Obliterans: Newer Concepts on the Physiopathology and Treatment, Am. J. Surg. **21**:260-271 (Aug.) 1933. (*b*) Rabinowitz, H. M., and Kahn, J.: Relationship of Phospholipin Metabolism to Thrombo-Angiitis Obliterans and Its Treatment, ibid. **31**:329-339 (Feb.) 1936. (*c*) Friedlander, M., and Silbert, S.: Thrombo-Angiitis Obliterans: VI. Chemistry of the Blood, Arch. Int. Med. **48**:500-506 (Sept.) 1931. (*d*) Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans: Reduction in Blood Volume, ibid. **45**:948-957 (June) 1930. (*e*) Bernhard, A.: Summary of the Chemical Blood Findings in Thrombo-Angiitis Obliterans, M. Rec. **97**:430-431 (March 31) 1920.

In a previous study [8] of the blood in peripheral circulatory diseases we observed an increased viscosity, a rapid coagulation and a dark, almost black color of the blood in cases of active thromboangiitis obliterans. Still more striking was the fact that the dark, venous blood from the diseased extremities was almost completely oxygenated and the carbon dioxide content in some cases was particularly low. With clinical improvement,[8a] there was a return to normal oxygen and carbon dioxide contents. It seemed to us that there existed a local or general disturbance in the dissociation of oxyhemoglobin or that the tissues were not using the oxygen supplied by the arterial blood. These observations sug-
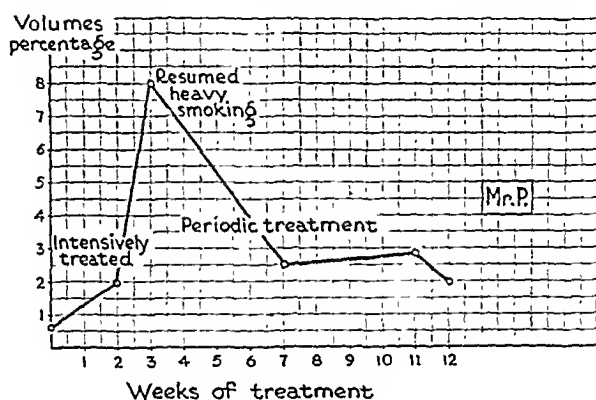
Chart 1.—Chart showing the oxygen unsaturation of the venous blood of the involved extremity of a patient with thromboangiitis obliterans. Oxygen unsaturation represents the difference between the actual oxygen content and the oxygen capacity of the blood. Normal arterial oxygen unsaturation is approximately 1 volume per cent and the average venous unsaturation 4.7 volumes per cent when the blood is withdrawn under conditions of rest. Mr. P., under stabilized conditions of rest had less than 1 volume of oxygen unsaturation of the superficial venous blood from the involved extremity as the initial determination, with an acute recurrence of the disease in the left leg. Under the same conditions, after intensive treatment the unsaturation increased to 8 volumes per cent. Subsequently, it decreased to 2 volumes per cent, and the patient admitted that he had resumed heavy smoking. Clinical improvement accompanied the evidence of increased utilization of oxygen in the superficial circulation. The right leg had been previously amputated for thromboangiitis obliterans.

8. Theis, F. V., and Freeland, M. R.: Peripheral Circulatory Disease: Effect of Alternating Positive and Negative Pressure Treatments on Venous Blood and the Skin Temperatures, J. A. M. A. **107**:1097-1104 (Oct. 3) 1936.

8a. The patients included in this report were treated with intravenous injections of sodium thiosulfate or of sodium tetrathionate. Since February 1937 we have used almost exclusively sodium tetrathionate prepared for us experimentally and supplied by G. D. Searle & Co., of Chicago.

gested the present study to determine more fully some of the physical and chemical properties of the blood which might help in the diagnosis and the treatment of the disease.

VISCOSITY

The appearance of the blood of patients with thromboangiitis obliterans, as well as the difficulty in withdrawing it, seems to demonstrate that its viscosity is increased. The comparative values of the viscosity of the blood of patients with thromboangiitis obliterans and of normal controls reported by Koga [5] are inaccurate because of the many variable factors in the blood.[9] An increased rate of sedimentation during the active stage of the disease interfered with the accepted Hess method [10] for determinations of viscosity. It was apparent that the passage of whole blood through the Hess tube was delayed by the rapid settling of the cellular constituents. Consequently, comparative values of the viscosity of the blood could not be established by capillary tube methods.

SEDIMENTATION TESTS

In attempting these tests for viscosity, we felt that some data on the sedimentation rate of patients with thromboangiitis obliterans should be available. The Linzenmeier method [11] was used, and from two to four hours or more was accepted as the time for 18 mm. of cells to settle in normal blood. Seven persons with active thromboangiitis obliterans had rates of from fifteen to forty-five minutes (table 1). No evidence of infection was present to account for the rapid sedimentation. In contrast, ten tests on clinically recovered or improved patients with thromboangiitis obliterans showed sedimentation rates as high as nine hours. Ten patients with other peripheral circulatory diseases had sedimentation rates varying from an hour and two minutes to more than five hours. The difference between the sedimentation rates of persons with acute or active thromboangiitis obliterans and those of improved or recovered patients seems to be of diagnostic and prognostic significance.

HEMATOCRIT TESTS

Increased cell volume due to anhydremia or to polycythemia was considered a possible factor in the increased viscosity and increased sedi-

9. Burton-Opitz, R.: The Viscosity of the Blood, J. A. M. A. **57**:353-358 (July 29) 1911. Samuels, S. S.: Diagnosis and Treatment of Diseases of the Peripheral Arteries, New York, Oxford University Press, 1931, p. 60.

10. Hess, W. R.: A New Apparatus for Determining Blood Viscosity, München. med. Wchnschr. **54**:1590-1591 (Aug. 6) 1907. Bircher, M. E.: Clinical Diagnosis by the Aid of Viscosity of the Blood and Serum, J. Lab. & Clin. Med. **7**:134-147 (Dec.) 1921.

11. Bray, W. E.: Synopsis of Chemical Laboratory Methods, St. Louis, C. V. Mosby Company, 1936.

mentation time. Accordingly, hematocrit tests were made to determine the actual percentage volume of cells and of serum. With a graduated tube, the blood was centrifuged for forty-five minutes at a predetermined rate to produce maximum packing of the cells. Observations (table 2) on patients with various types of peripheral circulatory diseases and on normal controls did not show a significant increase in cell volume for those with thromboangiitis obliterans. In general, a direct relation between the cell volume and the red cell count is to be expected if the

TABLE 1.—*Sedimentation Time of the Blood of Patients with Thromboangiitis Obliterans and with Other Peripheral Circulatory Diseases (Linzenmeier Method)*

		Time					
	No. of Patients	Maximum		Minimum		Average	
		Hr.	Min.	Hr.	Min.	Hr.	Min.
Thromboangiitis obliterans							
Acute or active stage	7	0	45	0	15	0	39
Improved or clinically recovered	10	9	30	1	5	3	54
Other peripheral circulatory diseases	10	5	45	1	2	3	0

TABLE 2.—*Hematocrit or Packed Cell Volume Percentage of Patients with Peripheral Circulatory Diseases*

	No. of Patients	Maximum Cell Vol. %	Minimum Cell Vol. %	Average Cell Vol. %
Controls—normals and others	40	54.00*	32.52	39.55
Thromboangiitis obliterans	40	50.53	33.83	43.25
With anemia	..	39.60	23.33	35.37
With polycythemia	..	70.73	40.49	46.06
Polycythaemia vera—no thrombosis	2	62.66	56.06	59.64
Thrombophlebitis				
Migrating	1	44.75	43.21	43.73
Spontaneous	6	45.76*	37.10	42.33
Arteriosclerosis				
Senile	9	40.00	34.07	36.45
Diabetic	1	.....	.....	39.60
Raynaud's disease and neurocirculatory diseases	10	44.26	33.19	38.05
Frostbite	4	41.33	38.20	39.86

* Heavy smokers.

size of the cells remains constant. This was usually found to be true except in the cases of thromboangiitis obliterans, in which high cell counts were frequently present with low cell volumes. One patient with repeated red cell counts over 5,500,000 had volume percentages under 35. Subsequently, with a normal cell count of 4,600,000, he had a normal cell volume of 40 per cent. The reverse of these conditions was also noted in that low cell counts occurred with a higher than normal cell volume. These observations in cases of thromboangiitis obliterans indicate that the size of the erythrocytes fluctuates during the course of the disease and that the increased viscosity of the blood is not due to high cell volume as a result of anhydremia or of polycythemia.

HEMOGLOBIN AND CELL COUNTS

The frequency of high red cell counts in the cases of thromboangiitis obliterans at some time during the period of observation suggested polycythemia as a stage of the disease (table 3). In the acute stage, the cell counts were usually around 4,000,000, while during the period of

TABLE 3.—*Hemoglobin Content and Blood Counts in Patients with Peripheral Circulatory Diseases*

Erythrocyte Counts of Patients with Thromboangiitis Obliterans

Patients	No. of Counts	Period of Observation, Months	In Millions		
			Maximum	Minimum	Average
Mr. Pl	6	2	6.35	5.30	5.90
Mr. V	4	5	5.15	4.12	4.49
Mr. P	2	12	4.85	4.67	4.76
Mr. A	8	13	6.04	4.80	5.40
Mr. Bo	9	39	5.62	4.36	5.01
Mr. S	2	1½	3.96	3.61	3.79
Mr. B	5	22	5.60	4.14	4.89
Mr. El	5	25	4.75	4.15	4.50
Mr. K	5	90	5.67	3.92	4.63
Mr. J	7	12	5.66	4.19	4.68
Mr. R	4	7	5.85	4.84	5.18
Mr. O	9	11	4.80	3.68	4.03
Mr. M	9	38	5.27	3.96	4.36
Mr. C	8	27	5.75	4.41	5.21
Mr. N	13	39	7.58	3.91	5.17
Mr. N	4	8	6.00	4.19	4.97
Mr. I	7	12	5.23	4.23	4.85
Mr. Sm	4	7	5.85	4.56	5.11
Mr. E	1	2	5.34	....	. ....
Mr. Ch	3	34	5.90	5.20	5.66
Mr. Al	2	1	5.41	5.11	5.26

	No. of Patients	No. of Patients with Maximum Counts (In Millions) Over				
		4.0	5.0	5.5	6.0	7.0
Thromboangiitis obliterans	21	4	4	9	3	1
Other peripheral circulatory diseases	65	46	10	0	0	0
Polycythaemia vera	2	0	0	0	1	1

Leukocyte Counts

	No. of Patients	No. of Patients with Maximum Counts Over		
		6,000	12,000	15,000
Thromboangiitis obliterans	20	3	15	2
Other peripheral circulatory diseases	49	41	7	1
Polycythaemia vera	2	2	0	0

Hemoglobin Determinations

	No. of Patients	No. of Patients with Percentage Over				
		80	90	100	105	110
Thromboangiitis obliterans	20	4	4	9	1	2
Other peripheral circulatory diseases	49	36	10	2	0	0
Polycythaemia vera	2	0	1	1	0	0

clinical improvement, normal counts or counts showing polycythemia were noted. Of 21 patients, 17, or 81 per cent, had one or more counts over 5,000,000; of these, 13, or 62 per cent, had counts over 5,500,000. One patient had two low red cell counts, but he was observed for less than two months. Of 65 persons with other circulatory diseases, only 10, or 15 per cent, had counts slightly over 5,000,000, and the counts of 9 persisted under 4,000,000. The condition of 2 patients was diagnosed

as polycythaemia vera with circulatory symptoms, but these patients were not included in the group of those with thromboangiitis obliterans because of the absence of thrombosis. The fact that the red cell counts of patients with thromboangiitis obliterans change during the course of the disease indicates a stage of anemia and a stage of polycythemia.

In the absence of infection, increased white cell counts usually accompany the higher red cell counts. Increase in both the red and the white cells would seem to be evidence of increased concentration of the blood in the stage of polycythemia but would not account for the greater viscosity of the blood or for the more rapid sedimentation during the acute stage of the disease when counts are normal or low.

Determinations of hemoglobin were made by the Newcomer method. Variations in the content of hemoglobin were found in the same patient with thromboangiitis obliterans without changes in red cell counts. High percentages were more frequent in patients with thromboangiitis obliterans than in normal controls or in patients with other circulatory diseases and usually accompanied normal cell counts and clinical improvement.

COAGULATION OF THE BLOOD

The rapid and firm coagulation of the blood of patients with acute thromboangiitis obliterans is particularly striking as the blood is emptied from a syringe. In a number of instances, the clotting occurred so quickly and so solidly that all efforts to remove the plunger from the syringe failed. With the use of fine capillary tubes, the coagulation time of patients with acute thromboangiitis obliterans was frequently found to be less than one minute, increasing to two or more minutes as the patient improved. The rapid clotting is not due to an increase of calcium in the serum, for the calcium and phosphorus in the serum were always within normal limits. Furthermore, in one determination of fibrinogen the content was below normal.

REACTION OF THE BLOOD

Changes in the reaction of the blood affect the size of the red corpuscles.[12] As previously described, changes in the size of the erythrocytes occur in thromboangiitis obliterans. Accordingly, a shift in the acid-base balance could produce such changes. Theoretic p_H's from Bock's monograms [13] were obtained by using the oxygen content and

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12. Price-Jones, C.: The Diurnal Variations in the Sizes of Red Blood Cells, J. Path. & Bact. **23**:371-383 (Dec.) 1920.

13. (*a*) Bock, A. V.; Dill, D. B.; Hurxthal, L. M.; Lawrence, J. S.; Coolidge, T. C.; Dailey, M. E., and Henderson, L. J.: Blood as a Physicochemical System: V. The Composition and Respiratory Exchanges of Normal Blood During Work, J. Biol. Chem. **73**:749-766 (June) 1927. (*b*) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Interpretations, Baltimore, Williams & Wilkins Company, 1932, vol. 1.

the carbon dioxide content of the blood. In 5 cases of acute thromboangiitis obliterans, the initial p_H thus obtained was 7.60 or higher. However, these values are greater than any that actually occur, because of buffer substances compensating for abnormal oxygen content and for abnormal carbon dioxide content. We are now able to get actual potentiometric p_H's, both with glass and with quinhydrone electrodes, which compare fairly accurately with the nomogram values. As a rule, the actual p_H is about 0.06 less than the aforementioned theoretic values. Our most recent determinations showed actual p_H's of 7.60, 7.62 and 7.64, with theoretic values beyond the range of the nomograms. A p_H of from 7.38 to 7.50 was uniformly obtained for normal controls, for clinically recovered or improved patients with thromboangiitis obliterans and for patients with other peripheral circulatory diseases. For patients with acute thromboangiitis obliterans, the p_H was consistently higher and above 7.55. Such changes in the reaction of the blood in long-standing conditions such as thromboangiitis obliterans, whether a cause or an effect of the disease, reflect a general shift of the buffer substances as well as changes in the metabolic processes of the body.

OXYGEN AND CARBON DIOXIDE CONTENTS OF THE BLOOD

Determinations of the oxygen and the carbon dioxide content of the blood were made by the Van Slyke technic [14] with and without reagents. Patients were stabilized at rest in bed for one hour or more, and, without the use of a tourniquet, the blood was withdrawn under oil from the antecubital vein at the elbow or from a branch of the internal saphenous vein at the knee. The specimens were immediately transferred to mercury tonometers, placed in a refrigerator and analyzed as soon as possible. All determinations were made in duplicate, and careful checks established the accuracy of the procedures. Difficulty in finding superficial veins in many patients with thromboangiitis obliterans made it impossible to obtain blood from both the arm and the leg in every case. The data included in the tabulations in table 4 pertain to patients from whom blood could be withdrawn from the involved extremity.

Gasometric Method with Reagents.—In a series of 7 patients with acute or recurrent thromboangiitis obliterans, determination of the oxygen and the carbon dioxide content of the venous blood from the involved extremity showed arterial oxygenation (table 4). Patients with other circulatory diseases and clinically recovered or improved patients with thromboangiitis obliterans had normal values with from 15 to 40 per cent oxygen unsaturation.[15] Usually, the uninvolved extremi-

14. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, vol. 2.

15. Lundsgaard, C.: Studies of Oxygen in the Venous Blood: I. Technique and Results in Normal Individuals, J. Biol. Chem. **33**:133-144 (Jan.) 1918.

ties had values which were either normal or lower than normal. The blood from the involved extremity should be studied because the oxygen and carbon dioxide contents in the arm usually differ from those in the leg of the same patient (table 5). In the presence of poor circulation, these conditions indicate a local disturbance in the utilization of oxygen in the involved extremity. In some instances, however, almost complete oxygen saturation of the venous blood from apparently unaffected extremities was also present, which indicated that high oxygen saturation of the venous blood may be either a local or a general condition.

Arterial oxygen content of the venous blood occurs either with a rapid flow of blood or with nonutilization of the oxygen supplied by the arterial blood. Meakins and Davies [16] demonstrated that submerging a normal extremity in water at 45 C. will increase the rate of blood flow so that the oxygen content of the venous blood is the same as
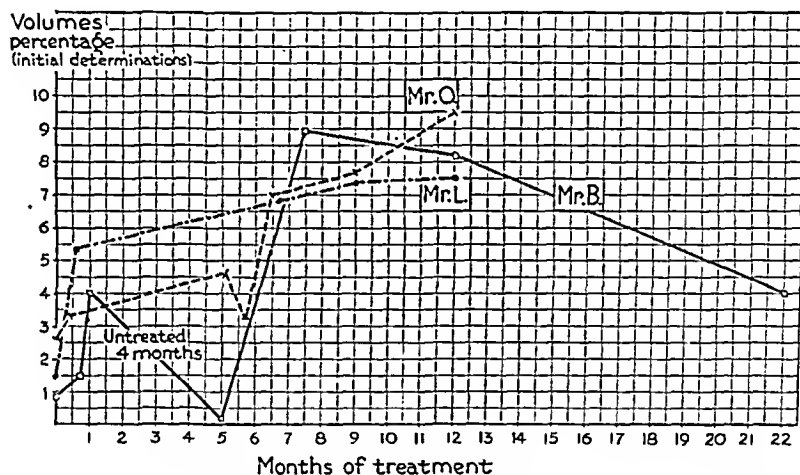
Chart 2.—Chart showing the oxygen unsaturation of the venous blood of the involved extremity of 3 patients with thromboangiitis obliterans. The curves represent the utilization of oxygen in the superficial circulation in the involved extremity under the same conditions as those described in chart 1. The 3 patients were observed for from twelve to twenty-two months, and the initial determinations on the venous blood were the same as those usually found in the arterial blood (table 4). With clinical improvement, normal or higher than normal oxygen unsaturation continued, except in the case of Mr. B. After four months without treatment, he had a painful recurrent ulcer on the first toe, and there was a return of the high oxygen saturation of the venous blood. Relief from pain and rapid healing of the ulcer accompanied greatly increased unsaturation of the venous blood. The almost complete oxygen saturation of the venous blood in the presence of poor circulation indicates nonutilization of oxygen by the tissues.

16. Meakins, J. C., and Davies, H. W.: Observations on the Gases in Human Arterial and Venous Blood, J. Path. & Bact. **23**:451-461 (Dec.) 1920.

that of the arterial blood. This condition of rapid blood flow was certainly not present in the cases of thromboangiitis obliterans. As shown in table 4, the subnormal stabilized skin temperatures taken by means of a

TABLE 4.—*Initial Determinations of Oxygen and Carbon Dioxide Contents of Venous Blood and Peripheral Skin Temperature of Involved Extremity of Patients with Thromboangiitis Obliterans and Other Peripheral Circulatory Diseases*

Initial Determinations for Patients with Acute Thromboangiitis Obliterans

	Involved Extremity	O_2 Capacity, Vol. %	O_2 Saturation, %	CO_2 Content, Vol. %	Average Temperature of Toes or Fingers
Mr. P.	L. leg	21.65	96.6	22.50	28.6 C.
Mr. R.	R. leg	20.38	95.8	37.74	25.2 C.
Mr. B.	R. leg	23.90	96.5	39.77	27.1 C.
Mr. C.	L. leg	21.10	98.0	46.66	30.0 C.
Mr. K.	R. leg	18.85	94.7	49.91	27.8 C.
Mr. M.	R. arm	19.00	92.7	42.30	26.7 C.
Mr. L.	L. leg	18.50	91.9	44.56	30.0 C.

Average Initial Determinations for All Subjects

	No. of Patients	O_2 Capacity, Vol. %	O_2 Saturation, %	CO_2 Content, Vol. %
Controls				
Normal	9	19.38	72.15	49.79
Others	7	19.30	69.28	49.89
Thromboangiitis obliterans				
Initial—untreated	7	19.97	95.32	40.53
Clinically recovered	11	18.13	62.53	49.83
Other peripheral circulatory diseases	19	18.17	68.05	48.56
Polycythemia—with peripheral circulatory symptoms but no thrombosis	2	22.48	73.95	46.71

TABLE 5.—*Difference in Oxygen and Carbon Dioxide Contents of the Venous Blood of the Leg and Arm of One Patient*

Date	Leg, Contents, Vol. %		Arm, Contents, Vol. %	
	O_2	CO_2	O_2	CO_2
3/23/36	11.61	45.75	8.68	48.77
4/ 6/36	14.81	39.95	9.34	43.40
4/ 7/36	13.79	41.39	8.68	41.68
4/ 8/36	9.07	45.84	5.13	48.40
4/13/36	18.00	37.10	8.54	44.47
Average	13.46	42.00	8.07	45.34

Tycos dermatherm [17] indicate a diminished flow of blood. With a diminished or sluggish flow, there should be more oxygen withdrawn from the blood and more carbon dioxide absorbed by the blood.[15] Accordingly, the reverse of what was actually found is expected in a sluggish circulation. Nonutilization of oxygen by the tissues would account for the arterial oxygen content of the venous blood in the pres-

17. Scott, W. J. M.: An Improved Electrothermal Instrument for Measuring Surface Temperature, J. A. M. A. **94**:1987-1988 (June 21) 1930.

ence of a low skin temperature. This agrees with Popoff's histologic study [18] that in thromboangiitis obliterans abnormal communications or anastomoses shunt the arterial blood directly into the veins without irrigating the capillaries of the tissues. However, our findings of the normal utilization of oxygen with clinical improvement do not support Popoff's irreversible process.

Vacuum Method.—In order to determine the stability of the oxygen and the hemoglobin in the blood, we studied the dissocation of the two by means of vacuum only. No reagents were used in the Van Slyke reaction chamber. For 15 controls, an average of 66.91 per cent of the oxygen was liberated; for 5 patients with thromboangiitis obliterans 68.70 per cent, and for 3 with arteriosclerosis, 58.04 per cent. These results showed that in the cases of thromboangiitis obliterans the oxyhemoglobin in the blood released a normal amount of oxygen when subjected to vacuum only.

METHEMOGLOBIN

The initial high oxygen saturation and the dark color of the venous blood in the involved extremity of the patients with thromboangiitis obliterans suggested the possibility of some inactive form of oxygen and hemoglobin. One form, methemoglobin, is dark colored and liberates its oxygen much less readily than does oxyhemoglobin.[19] Results of spectroscopic examinations were repeatedly negative for methemoglobin, but less than 25 per cent methemoglobin has been reported as insufficient concentration[20] to be discernible spectroscopically. Therefore, ten quantitative determinations were made by the Stadie method.[21] The occasional presence of small amounts of methemoglobin was too insignificant for it to be a factor in the abnormal condition of the blood in thromboangiitis obliterans.

METABOLISM TESTS

It seemed questionable whether these observations of disturbed utilization of oxygen would materially affect the total oxygen consumption of the body and, consequently, the basal metabolic rate. However,

18. Popoff, N. W.: The Digital Vascular System, with Reference to the State of the Glomus in Inflammation, Arteriosclerotic Gangrene, Diabetic Gangrene, Thrombo-Angiitis Obliterans and Supernumerary Digits, Arch. Path. **18**:295-330 (Sept.) 1934. ·

19. Conant, J. B., and Fieser, L. F.: Methemoglobin, J. Biol. Chem. **62**:595-622 (Jan.) 1924. Conant, J. B., and Scott, M. D.: The So-Called Oxygen Content of Methemoglobin, ibid. **69**:575-587 (Aug.) 1926. Anson, M. L., and Mirsky, A. E.: On Hemochromogen and the Relation of Protein to the Properties of Hemoglobin, J. Physiol. **60**:50-67 (May 21) 1925.

20. Kobert, R.: Lehrbuch der Intoxikationen, ed. 2, Stuttgart, Ferdinand Enke, 1902, vol. 1, p. 97; cited by Peters and Van Slyke,[12b] p. 635.

21. Stadie, W. C.: Method for Determination of Methemoglobin in Blood, J. Biol. Chem. **41**:237-241 (Feb.) 1920.

Silbert and Friedlander [22] reported low metabolic rates for 50 unselected patients with thromboangiitis obliterans, and for none was the rate above zero; the average for smokers and nonsmokers was — 16 per cent. In the absence of infection or of severe pain, the rates for our patients were as low as — 27 per cent, and all were persistently below zero. Coller and Maddock [23] studied the relation of metabolic rates to peripheral temperatures and stated that low body metabolism probably accounts for low peripheral skin temperatures. Our results confirm the presence of low basal metabolic rates in cases of uncomplicated thromboangiitis obliterans.

COMMENT

The increased viscosity and the rapid clotting of the blood in acute thromboangiitis obliterans may be the important factors in the complex physiology of the blood which leads to thrombosis. Meyer [6b] advised treatment with a solution of sodium citrate to overcome the rapid clotting; whether the various salt solutions act as anticoagulants, as diluents or by shifting the acid-base balance in the blood and tissues has not been determined. The adequacy or availability of oxygen in the internal organs of the body influences the rapidity of coagulation. Rapid clotting during asphyxia, according to Cannon and Mendenhall,[24] is the result of deficient oxygen supply; and Gray and Lunt [25] attributed the rapid coagulation which follows moderate hemorrhage as due to the same deficiency. Accordingly, the evidence of anoxia or disturbed utilization of oxygen here presented should affect the coagulation of the blood and contribute to thrombus formation.

Anoxia, or lack of oxygen, in the tissues of the involved extremity of patients with acute thromboangiitis obliterans is not due entirely to arterial occlusion. The almost complete oxygen saturation of the superficial venous blood indicates either a failure of the arterial blood to irrigate the tissues or an inability of the tissue cells to utilize the oxygen supply. The normal utilization of oxygen by improved or recovered patients does not support Popoff's [18] irreversible process of direct arterial-venous shunting of the blood in this disease. Rest pains and intermittent claudication are clinical evidence of the oxygen want; the severity of the symptoms is frequently out of all proportion to the

22. Silbert, S., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans: The Basal Metabolism, J. A. M. A. **96**:1857-1858 (May 30) 1931.

23. Coller, F. A., and Maddock, W. G.: Function of Peripheral Vasoconstriction, Ann. Surg. **100**:983-992 (Nov.) 1934.

24. Cannon, W. B., and Mendenhall, W. L.: Factors Affecting the Coagulation Time of Blood, Am. J. Physiol. **34**:243-250 and 251-261 (March) 1914. Cannon, W. B., and Gray, H.: Factors Affecting the Coagulation Time of Blood, ibid. **34**:232-242 (March) 1914.

25. Gray, H., and Lunt, L. K.: Factors Affecting the Coagulation Time of Blood, Am. J. Physiol. **34**:332-351 (June) 1914.

oxygen want of the tissues, due to arterial occlusion [26] or to the degree of circulatory deficiency.

The normal or anemic blood cell counts during the painful stage of the disease are replaced by higher red cell counts during the stage of recovery. This important compensatory reaction of the hemopoietic system to oxygen want in other diseases has been thoroughly studied by Barcroft.[27] Eighty-one per cent of our patients had erythrocyte counts of from 5,000,000 to 7,500,000. In other types of peripheral circulatory diseases, irrespective of the degree of oxygen deficiency or of gangrene due to arterial occlusion, red cell counts were rarely above normal and usually continued below normal. In thromboangiitis obliterans these apparently compensatory changes in red cell counts have not been considered in relation to the stages of the disease. According to Piney,[28] low red cell counts may occur in polycythaemia vera, and Lamson [29] described red cell counts over 5,000,000 as indicative of polycythemia, oxygen want being the fundamental cause [30] of the increased cell counts. The similiarity of polycythaemia vera and thromboangiitis obliterans as observed in the hematologic clinic of the New York Hospital has been reported recently.[31] Pernokis [32] found that peripheral circulatory symptoms were present in 75 per cent of his cases of polycythaemia vera. The frequency of arterial thrombosis in polycythaemia vera is more generally known than is the occurrence of secondary polycythemia in thromboangiitis obliterans.

Fluctuation in the size of the erythrocytes occurs in thromboangiitis obliterans, which is probably due to changes in the reaction of the blood. In the acute stage, the blood is more alkaline than in any other stage, but the carbon dioxide–combining power of the blood as an index of acid-base balance is not above normal limits. Normally, the cell volume

26. Theis, F. V.: Artery and Concomitant Vein Ligation in Surgery of the Large Blood Vessels, Arch. Surg. **17**:244-258 (Aug.) 1928. Horton, B. T.: A Study of the Vessels of the Extremities by the Injection of Mercury. S. Clin. North America **10**:159-170 (Feb.) 1930. Brown, G. E.: Thrombo-Angiitis Obliterans, Surg., Gynec. & Obst. **58**:297-309 (Feb. 15) 1934.

27. Barcroft, J.: The Respiratory Function of the Blood, London, Cambridge University Press, 1925, vol. 1; 1928, vol. 2.

28. Piney, A.: Diseases of the Blood, Philadelphia, P. Blakiston's Son & Co., 1932, p. 160.

29. Lamson, P. D.: Polycythemia, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1920, vol. 4: Role of the Liver in Acute Polycythemia, J. Pharmacol. & Exper. Therap. **7**:169-224 (July) 1915.

30. Fitz, R.: Polycythemia, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1924, vol. 2.

31. Reznikoff, P.; Foot, N. C., and Bethea. J. M.: Etiologic and Pathologic Factors in Polycythemia Vera, Am. J. M. Sc. **189**:753-759 (June) 1935.

32. Pernokis, E. W.: Blood Studies, J. A. M. A. **108**:1686-1690 (May 15) 1937.

percentage is related to changes in the cell counts. However, in thrombo-angiitis obliterans the high, or polycythemic counts with lower than normal cell volume do not support the opinion [7d] that the increased viscosity of the blood is due to anhydremia, unless the size of the red cells is reduced to a greater extent than the reduction in serum volume.

Other blood changes [7] have been reported. We have been able to confirm the observations of Rabinowitz and Kahn on disturbed phospholipin metabolism, of Silbert and Friedlander on cholesterol and of Bernhard on disturbances in sugar metabolism. Four of our patients had transient glycosuria with normal blood sugar. These observations, as well as the success of treatment with intravenous solutions, are predominantly in favor of naming disturbed physiology of the blood, leading to increased coagulation and formation of thrombi, as the important underlying condition in thromboangiitis obliterans.

The diagnosis of thromboangiitis obliterans, either clinical or pathologic, is based primarily on the presence of peripheral arterial occlusion. Autopsy [33] has demonstrated the distribution, the extent and the characteristics of the vascular lesions, but the cause of the thromboses is not explained by the pathologic changes. The majority of patients have the recurrnet progressive disease described by Buerger; [4] the condition in many cases remains permanently arrested or cured. , We have no reason to assume that the disease is due to the same cause in all instances. Goodman's [34] contention that thromboangiitis obliterans is caused by the Rickettsia of typhus fever is untenable. In 6 cases included in this investigation, cutaneous tests with antigen supplied by Goodman were all negative.

Our purpose in this investigation was to find some means of making an early diagnosis, to evaluate the effectiveness of treatment and to determine when the disease has been arrested. Those factors in the complex physiology of the blood which seemed most pertinent to the clinical and pathologic pictures of the disease were included in this investigation. We believe that the definitely pathologic condition of the blood during the acute or painful stage of the disease, which for the most part returns to normal with clinical recovery, offers a sound basis for future study. Further studies we are now making should disclose other changes in the blood and some of the factors controlling local oxidation of tissue.

33. Morgan, J. R. E.: Thrombo-Angiitis Obliterans: Distribution of the Lesions in the Vessels of the Leg, Arch. Path. **18**:216-224 (Oct.) 1934. Telford, E. D.. and Stopford, J. S. B.: Thrombo-Angiitis Obliterans, Brit. M. J. **2**:1035-1037 (Dec. 6) 1924. Buerger.[4]

34. Goodman, C.: Thrombo-Angiitis Obliterans and Typhus: Evidence of Etiologic Relationship, Arch. Surg. **35**:1126-1144 (Dec.) 1937.

SUMMARY AND CONCLUSIONS

In a series of 7 cases of acute thromboangiitis obliterans in which the superficial venous blood from the involved extremity could be studied, we found increased viscosity of the blood, rapid sedimentation of the cells, rapid coagulation, greatly increased alkalinity, low or normal cell counts and arterial oxygen saturation and a low carbon dioxide content of the blood.

In 21 clinically improved or recovered patients with thromboangiitis obliterans, in normal controls, and in patients with other peripheral circulatory diseases, these conditions were not present.

Clinical improvement with relief from rest pains in cases of thromboangiitis obliterans is accompanied by normal oxygen saturation of the venous blood and usually by a normal or polycythemic blood count.

With recurrence of the disease, we found a return to the high oxygen saturation of the venous blood.

These results suggest that a disturbance in the utilization of oxygen is one of the conditions in the complex physiology of the blood and tissue metabolism which are responsible for the acute symptoms of thromboangiitis obliterans.

At present, a thorough study of the chemical and physical properties of the blood is necessary (1) to make an early diagnosis of thromboangiitis obliterans, (2) to evaluate the effectiveness of treatment and the harmful effect of contributing factors such as smoking, (3) to detect recurrences, and (4) to determine when the disease has been arrested.

SERUM THERAPY FOR STREPTOCOCCIC INFECTION OF THE NOSE, THROAT AND EAR AND ITS COMPLICATIONS

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In our earlier series [1] of 26 patients treated with serum, 8 were allocated to the category of patients with diseases of the ear, nose and throat. Cultures of the blood of 6 of these yielded bacteria. Two died and 6 survived. In our present additional group of 66 patients, data on whom were tabulated in the immediately preceding paper of the present series, 30 patients were assigned to this category, including patients with pneumonia, empyema and mediastinitis. Their cases will here be designated by the serial numbers employed in the general tabulation in the preceding paper of this series.[2]

CASE 29.—R. C., a boy aged 14, contracted a head cold on Oct. 16, 1933, and later had purulent otitis media. About October 25 the temperature rose to 105 F. and remained high until the boy's admission to the hospital, on October 30. A culture of blood taken on October 28 gave a positive growth of hemolytic streptococci. A mastoidectomy on the right side had been done in 1930. A culture of blood taken October 30 again yielded bacteria, and on October 31 the concentrated streptococcus serum of the New York state department of health was given, the total amount being 18,900 units. A mastoidectomy on the left revealed a thrombus in the left lateral sinus. The left internal jugular vein was ligated, and a transfusion of 260 cc. of blood was given. Intravenous serum treatment was continued; 60,000 units was given on November 1; 20,000 units on November 2; 20,000 units on November 3; 60,000 units on November 4; 40,000 units on November 5, and 40,000 units on November 6. A culture of blood taken on this day remained sterile, and because of this fact and the distressing urticaria the serum was discontinued. However, a culture of blood taken on November 8 gave a positive growth on November 9, and the serum was again given, in divided

1. Sheplar, A. E.; Spence, M. J., and MacNeal, W. J.: Therapeutic Use of the Concentrated Streptococcus Serum of the New York State Department of Health in Patients with Infections of the Ear, Nose and Throat, Arch. Surg. 30:1-13 (Jan.) 1935.

2. Sheplar, A. E.; Spence, M. J., and MacNeal, W. J.: General Observations on the Serum Therapy of Infections with Streptococcus, Arch. Surg. 35:772-789 (Nov.) 1938.

doses, to a total of 30,000 units. Severe cyanosis and dyspnea occurred in spite of care in administration. The serum was continued daily until November 16. On November 29 an abscess of the right arm was incised, and the pus contained hemolytic streptococci. A transfusion of 180 cc. was given. On December 3 a small abscess in the right groin was aspirated; it yielded pus containing staphylococci. On December 7 a thoracentesis on the left yielded 250 cc. of fluid containing hemolytic streptococci, but this empyema cleared without further drainage. A transfusion of 200 cc. was given on December 11. The patient was discharged December 24 and has remained well up to the time of writing. A total of 355,400 units of New York state concentrated serum was used.

CASE 33.—B. F., a boy aged 5 years, was admitted to the hospital Jan. 12, 1934, with otitis media on the left. Spinal tap on January 12 yielded fluid containing hemolytic streptococci. The concentrated streptococcus serum was given by intrathecal and intravenous injection from January 14 to January 21, to a total of 460,000 units. The patient died on January 23, and necropsy revealed generalized purulent meningitis and bronchopneumonia of the lower lobe of the right lung.

CASE 34.—C. F., a boy, born July 30, 1932, had a history of mastoidectomy on the right in December, at the age of 5 months. Subsequently there was slowly progressive osteomyelitis of the skull, which was found to be due to Staphylococcus aureus. The treatment of this condition is not of concern here, but on Jan. 17, 1934, complicating purulent otitis media on the left side, caused by Streptococcus haemolyticus, was recognized. The grave condition of the patient precluded operative intervention. The concentrated streptococcus serum (New York state) was given daily from January 17 to 26, to a total of 18,900 units, and the left ear healed promptly.

CASE 37.—K. B., a girl aged 7 years, was admitted to the hospital Feb. 12, 1934. The right ear drum had been incised on January 29, and since February 8 there had been several chills and a rise of temperature to 106 F. The left hip was rigid and tender. Cultures of blood taken on February 12, 13 and 14 gave positive growth of hemolytic streptococci. A mastoidectomy on the right was performed on February 13, and a transfusion of 350 cc. of blood was given. The administration of concentrated streptococcus serum (New York state) was started on February 14 and continued daily to February 22, except for one day (February 18), the total amount being 240,000 units. The general progress was favorable, and the patient was able to sit in a wheel chair on March 3. The left hip continued painful, and a roentgenogram revealed epiphysitis at the upper end of the left femur. Aspiration and drainage of the left hip joint on March 15 yielded 60 cc. of pus containing streptococci. The patient was discharged on April 9, with a plaster dressing still in place.

CASE 39.—J. M., a boy aged 10 years, was seen in consultation at a hospital in Westchester County on April 7, 1934. He had had purulent otitis media on the right on March 14, and a culture of material from this ear was reported as yielding staphylococci. Culture of material taken from the throat at the same time showed predominant streptococci. On April 1 there was double vision in the right eye. A simple mastoidectomy on the right released a considerable amount of pus. After the operation the temperature reached 105.6 F. On April 6 there were signs of meningeal irritation, and spinal puncture yielded cloudy fluid containing 1,650 leukocytes per cubic millimeter. A culture of this fluid remained sterile. When the patient was seen on April 7 his condition was considered

desperate. The spinal fluid on this day contained about 2,000 white cells per cubic millimeter, but bacteria could not be recognized in it by microscopic study and the cultures remained sterile. The mastoidectomy wound was explored, with exposure of the lateral sinus and of the dura. This wound was irrigated with staphylococcus bacteriophage. Concentrated streptococcus serum (New York state) was given, 10 cc. into the spinal canal and 10 cc. intravenously. A transfusion of 200 cc. of blood was also given. On April 8 the spinal fluid was bloody and contained 2,800 white cells per cubic millimeter. The intraspinal and intravenous doses of streptococcus serum were repeated. On April 10 an intravenous injection of 10 cc. of serum was given. On April 12 the spinal fluid contained 1,050 white cells per cubic millimeter. Another intraspinal injection of 10 cc. of serum was given. On April 14 the temperature came down to normal, and the patient made a complete recovery. All cultures of the spinal fluid remained sterile. The precise condition within the skull remains, therefore, somewhat uncertain. It would seem from the clinical evidence that the infection was probably due to Str. haemolyticus and that it was close to the establishment of a generalized infection of the meninges when the serum treatment was started.

CASE 42.—L. I., a girl aged 4½ years, was admitted to the hospital on June 4, 1934, with a history of discharge from the right ear for two weeks and also of vomiting, fever and pain in both ankles, the right calf and the left knee for the last five days. On June 4 the temperature reached 105.6 F., and a culture of blood taken on this day gave an abundant growth of Str. haemolyticus. Daily cultures of the blood on June 5, 6, 7 and 8 yielded bacteria but a culture of blood taken June 9 remained sterile. On June 5 a mastoidectomy and ligation of the jugular vein were performed on the right and a transfusion of 135 cc. of blood was given. Concentrated streptococcus serum (New York state) was given intravenously, 40,000 units on June 6, 20,000 units intravenously and 20,000 units into muscle on June 7, 80,000 units intravenously on June 8 and 40,000 units on June 9. Because of the sterility of the culture the serum was now discontinued. Severe urticaria appeared on June 11 and persisted for two days. The patient appeared improved. After a transfusion of 200 cc. of blood on June 16 the temperature rose to 102.2 F., and a culture of blood taken on June 18 again revealed streptococci in the blood stream. Another culture, made on June 20, likewise yielded bacteria. A transfusion of 200 cc. of blood was given on June 21. Arthritis of the left hip and left knee was treated by traction and immobilization in a plaster dressing. The patient was discharged on July 26, without any disability. The total amount of serum used was 200,000 units.

CASE 48.—E. C., a man aged 30, was admitted to the hospital on Sept. 29, 1934, at which time an abscess of the thyroid gland was incised and drained. At this time roentgenographic examination indicated a tumor in the superior mediastinum. The patient was again admitted on October 14, at which time a tracheal intubation was done and a second abscess, between the trachea and the manubrium sterni, was incised and drained. He was discharged on October 20 and returned on November 18, at which time the wound was reopened and drained. Discharged on November 23, he returned again on November 26. More pus was evacuated through the wound above the manubrium sterni. Culture of the pus showed predominating hemolytic streptococci, smaller numbers of staphylococci and diphtheroids. A roentgenogram taken on November 27 revealed a mediastinal mass with a large cavity in it. On November 28 the patient was dyspneic and uncomfortable. His temperature reached 104 F. A culture of blood taken at this time remained sterile. On November 29 concentrated streptococcus serum (New York state) was given

in eight progressively increasing doses to a total amount of 40,000 units, and the abscess was irrigated through the cervical opening with a mixture of staphylococcus and streptococcus bacteriophages. No more serum was given, but the irrigations with bacteriophage were continued. There was gradual improvement. However, on December 3 roentgen examination disclosed a pleural exudate, and on December 4 a thoracentesis yielded 750 cc. of thin fluid containing hemolytic streptococci. A second thoracentesis, on December 10, yielded 15 cc. of yellow fluid. On December 12 the patient was out of bed. The wound in the neck was healing, and he was discharged on December 16 in good condition. The result in this case was unexpectedly gratifying. In October 1935 we heard from him at another hospital, where a diagnosis of lymphosarcoma had been made.

CASE 50.—J. B., a woman aged 80, was admitted to the hospital on Jan. 4, 1935, with a "running ear" which had opened spontaneously on Nov. 26, 1934. On Jan. 6, 1935, a simple mastoidectomy was performed on the left, and pus containing hemolytic streptococci was found. After the operation the temperature rose, reaching 103.8 F. on January 7 and 106 F. on January 9. A culture of blood taken on January 9 remained sterile. On the same day the spinal fluid contained 2,500 cells per cubic millimeter, and streptococci were visible on direct microscopic examination. Two days later, on January 11, concentrated streptococcus serum (New York state) was given in divided doses to a total of 10,000 units. A rather severe reaction to the serum required the injection of epinephrine. On January 12 she received 8,000 units, and on January 13, an intramuscular injection of 10,000 units and 10,000 units intravenously. This was followed by trembling of the entire body and moderate cyanosis. On the afternoon of this day she lapsed into coma, and she died at 2:40 a. m. January 14. Necropsy revealed purulent cerebrospinal meningitis. The total amount of serum used was 38,000 units.

CASE 52.—J. Z., a boy aged 1 year, was admitted to the hospital Jan. 10, 1935, with a temperature of 103.2 F. He had been ill with rhinitis since December 26 and with pneumonia since December 28. On January 10 a bilateral myringotomy was performed. On January 11 a culture of the blood was made, which gave a growth of hemolytic streptococci. The temperature had reached 104.6 F. On January 12 an abscess on the anterior aspect of the right forearm was incised; it yielded 30 cc. of thick green pus. A similar abscess in the occipital region was incised, and 10 cc. of pus was obtained from it. Both specimens contained streptococci. A transfusion of 250 cc. was given, and 40,000 units of concentrated streptococcus serum (New York state) was administered intramuscularly. On January 13 the patient was given additional serum (40,000 units) intravenously. A culture of blood taken on this day remained sterile. On January 14 a transfusion of 100 cc. was given, and on January 15, another intravenous dose of 40,000 units of concentrated serum. A blood culture made on this day remained sterile. On January 16 myringotomy and simple mastoidectomy were done on the left. The pus found during these operations yielded pneumococci. The temperature continued to range between 100.8 and 102.4 F. On January 18 roentgen examination revealed distention of the left hip joint with separation of the head of the femur. Serum rash appeared on January 20. On January 23 the left hip was opened, and 20 cc. of pus was obtained. A culture of this pus yielded Str. haemolyticus. From January 31 to February 5 the temperature remained below 99 F., but on February 5 it ascended to 103.4 F. and continued to spike daily until February 23. Cultures of blood taken February 11 and February 21 remained sterile. A roentgenogram taken on February 18 revealed destructive osteomyelitis

of the hip. On March 28 the incision of the femur and hip was extended to promote drainage. Culture of the exudate yielded hemolytic streptococci. A culture of blood taken April 1 remained sterile. After April 20 the temperature remained normal, and the patient was discharged with a draining sinus on April 23. The total amount of concentrated serum used was 120,000 units, and of blood given by transfusion, 1,100 cc. When serum therapy was discontinued culture of the blood was already sterile and the child's life seemed secure, but perhaps if we had persisted longer in the administration of the serum the patient might have been spared some of the serious complications.

CASE 53.—R. N., a man aged 62, was admitted to the hospital Feb. 8, 1935, with an ear which had been discharging since Dec. 8, 1934. Simple mastoidectomy on the left side was done on February 8, and culture of material from the mastoid yielded hemolytic streptococci. On February 10 the patient had a chill, and culture of blood taken on February 11 yielded twelve colonies of streptococci per cubic centimeter of blood. On February 12 the jugular vein was ligated on the left and the mastoid wound was reopened. On February 13 a transfusion of 500 cc. was given. On February 14 respirations were rapid; there was evidence of pneumonia and the left knee was painful. On February 15 a transfusion of 250 cc. of blood was given. The temperature was 105 F. A culture of blood taken on this day again showed hemolytic streptococci. On this date concentrated streptococcus serum was given, 20,000 units intravenously. Culture of blood taken on February 16 yielded more than 400 colonies per cubic centimeter of blood. On this day the patient was given 20,000 units of serum intravenously. On February 17 he was given 40,000 units of serum intravenously. Death occurred at 9 a. m., February 17. The total amount of serum used was 100,000 units. Early administration of the serum would seem to promise better results in such a case.

CASE 55.—R. A., a boy aged 13 months, was admitted to the hospital Feb. 16, 1935, with pharyngitis and an abscess in the left anterior cervical region, which had been present for two weeks. Incision of the abscess on February 18 released pus containing hemolytic streptococci. The temperature had remained between 102 and 103.8 F. but rose to 104 F. on February 25 and February 28. A culture of blood taken on March 1 gave a positive growth of the same type of streptococci. Subsequent cultures, made on March 3, 4, 5, 7, 9 and 13, produced the same organism, but the one taken on March 18 remained sterile. The child's temperature fell to normal and did not exceed 100 F. after March 11, so that the fact that a culture of blood taken on March 13 yielded bacteria is rather remarkable. Unconcentrated streptococcus serum (New York state) was administered, 10,000 units intravenously on March 2, and on March 3 the concentrated serum 20,000 units intravenously, was given. The same dose was administered on March 4, 40,000 units on March 5 and 20,000 units each on March 6, 7 and 8, when serum was discontinued. Serum rash appeared on March 10 and became generalized on March 11. Then the temperature fell to normal. The child was discharged in good condition on March 20. The total amount of serum used was 170,000 units.

CASE 56.—M. B., a boy aged 6 years, was admitted to a hospital in Westchester County, N. Y., on Feb. 27, 1935, with acute otitis media on the right and a temperature of 104 F. Myringotomy was performed on February 27 and mastoidectomy March 4. A culture of blood, taken on March 4, yielded hemolytic streptococci, and the infection of the blood stream persisted until death. Twelve transfusions were given at intervals of four days. Concentrated streptococcus serum (New York state) was given on March 4, 5, 7, 8, 10 and 14, to a total of 140,000 units.

Serum was discontinued after March 14. About two weeks later bronchopneumonia with multiple abscesses of the lung was recognized, and the child died on April 5.

CASE 61.—J. G., a girl aged 4 months, was admitted to the hospital March 30, 1935, with fluctuating swelling of the right cervical and the upper thoracic region, complicating an infection of the upper part of the respiratory tract, of two weeks' duration. The swelling was incised, and a large amount of pus was released on the day of admission. Culture of the pus yielded Staphylococcus aureus. Bilateral myringotomy was done on April 3, and this bilateral operation was repeated on April 12. On the next day the temperature reached 104.4 F. A culture of blood taken on this day remained sterile. On April 19 there was generalized erythema, and the temperature ranged between 100 and 101 F. On April 25 the temperature rose to 103.6 F., and on April 26 bilateral simple mastoidectomy was performed. Exudate from both mastoids yielded cultures of hemolytic streptococci. On the next day, April 27, the temperature reached 104 F. A culture of the blood was made, and this yielded a growth of hemolytic streptococci. On April 29 spinal tap yielded normal fluid, and culture of blood taken on this day remained sterile. The following night the temperature rose to 105 F., and culture of blood taken on April 30 gave a positive growth of hemolytic streptococci. Concentrated streptococcus serum (New York state) was given, 20,000 units in divided doses on April 29, by intracutaneous, subcutaneous, intramuscular and intravenous routes; 20,000 units intravenously on each of the next three days, April 30, May 1 and May 2; on May 3, an intravenous injection of 15,000 units, and on May 4, 5,000 units subcutaneously. The child improved rapidly. Cultures of blood taken on May 1 and May 2 remained sterile, and the patient was discharged in good condition on May 7. The total amount of serum used was 100,000 units.

CASE 62.—W. F., a boy aged 5 months, was admitted to the hospital on April 30, 1935, with purulent rhinitis and redness and swelling of the face, the neck and the upper part of the thorax, diagnosed as erysipelas. On May 1, erysipelas antitoxin (Squibb) was injected intramuscularly in divided doses to a total amount of 10.5 cc., and this dose was repeated on May 2. A culture of blood taken on May 2 gave a positive growth of hemolytic streptococci. On May 3 a transfusion of 150 cc. was given by the Unger method. The child was treated with ultraviolet rays for two minutes and was given 10,000 units of concentrated streptococcus serum (New York state) on May 3 and again on May 4. On May 5 there was evidence of bronchopneumonia. Concentrated streptococcus serum (New York state), 20,000 units, was given by intramuscular injection. A culture of blood taken on this day remained sterile, and the clinical condition seemed more satisfactory. On May 6, an intravenous injection of 5,000 units of unconcentrated streptococcus serum (New York state) was given, and this dose was repeated on May 7. The child died on May 8. Permission for necropsy was not obtained.

CASE 63.—L. S., a boy aged 5 years, was admitted to the hospital May 8, 1935, with a temperature of 105 F., a stiff neck and earache present since May 5. Bilateral myringotomy was performed on May 8, and on May 9 a spinal tap yielded normal fluid. Culture of blood taken on this day yielded two colonies per cubic centimeter of blood. On May 10 both ear drums were again incised. On May 11 the growth in the culture made on May 9 was recognized. At clinical consultation it was evident that the child had bilateral otitis with severe mastoiditis, metastatic abscess on the dorsum of each hand, rapid pulse and a dilated heart without recognizable murmur. The possibility of vegetative endocarditis

was given serious consideration, and the otologist felt that the child was not in good condition for a mastoidectomy and recommended that operation be deferred. Serum therapy was therefore requested and was instituted on May 11. An intracutaneous injection of 0.05 cc. of concentrated streptococcus serum (New York state) was given as a test for sensitiveness. The reaction was negative. This test was followed at thirty minute intervals by administration of 1.5 cc. of serum subcutaneously, 3.5 cc. intramuscularly, then 1 cc. intravenously and later 9 cc. intravenously, making a total of 40,000 units in the five doses. A culture of blood taken on this day remained sterile. The swelling on the dorsum of the right hand had increased considerably. On May 12 the child was given a transfusion of 250 cc. at 10 : 21 a. m. and an intravenous injection of 20,000 units (1 ampule) of con-
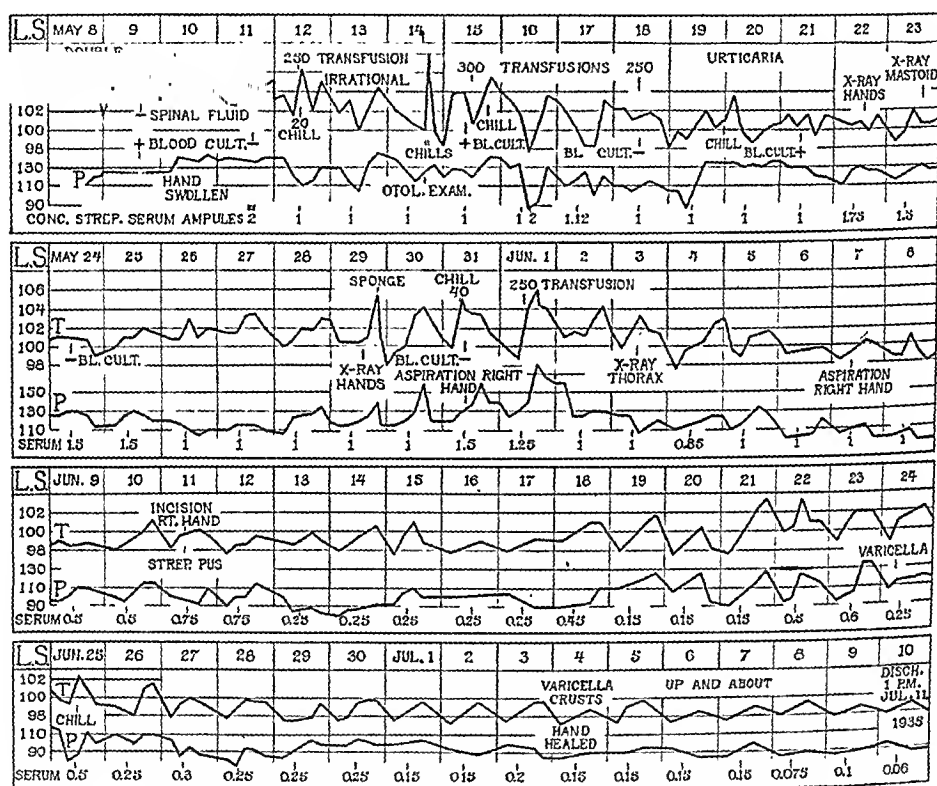
Chart 1 (case 65).—Abridged clinical record of L. S., a boy aged 5 years. The illness began with stiff neck, earache and high temperature. Culture of blood taken on May 9 yielded streptococci. Clinically the child had severe mastoiditis, a metastatic abscess on the dorsum of each hand and a dilated heart. Operation was deferred on account of his bad condition, and serum therapy was instituted May 11. The patient had a stormy course, but the record indicates what may be expected when serum is persistently administered over a long period.

centrated serum at 10 : 58 a. m. At 11 : 20 a. m. he had a shaking chill which lasted twenty minutes, with a rise of temperature to 106.2 F. at 12 noon. A culture of blood taken on May 15 yielded streptococci. The dose of serum was increased to three ampules (60,000 units) on May 16. A culture of blood taken on May 18 remained sterile, but culture of that taken on May 21 yielded bacteria. The serum was again increased for four days. On May 22 the record of this patient was presented before the clinical conference, and the general opinion was

discouraging. The sluggish abscesses on the dorsal surface of each hand persisted. Roentgenograms taken on May 22 and on May 29 revealed no evidence of disease of the metacarpal bones. Early in the morning of May 31 the patient had a chill lasting forty minutes. Soon after the chill, a culture of the blood was made (8:48 a. m.), and this remained sterile. At 8:55 a. m. the abscess on the back of the right hand was aspirated, and 3 cc. of thick pus containing streptococci was obtained. This abscess cavity was irrigated with streptococcus bacteriophage. A transfusion of 250 cc. of blood on June 1 was followed by a chilly sensation and a rise of temperature to 106 F., with a pulse rate of 180. On June 2 there were signs of fluid in the left pleural cavity, but roentgenographic examination on June 3 gave negative results, and thoracentesis was not done. The back of the right hand was incised and pus liberated on June 11. The abscess on the back of the left hand resolved without drainage. The dose of serum was decreased for the sake of economy in the period from June 9 to June 21 but was then increased for a few days during the febrile stage of chickenpox, which required segregation of the patient. Serum was then continued in smaller doses until July 11, when the patient was discharged. He was seen from time to time and was readmitted to the hospital on Jan. 20, 1938, with acute purulent otitis media caused by Str. haemolyticus, which has healed rapidly without complications.

CASE 68.—M. M., a girl aged 4 years, was admitted to a hospital in New Jersey on June 2, 1935, with a temperature of 106 F. and a history of sore throat since May 18, fever since May 28, abscess on the right side of the neck on May 29 (incised May 31) and myringotomy on the right on June 1. A culture of blood taken on June 2 yielded hemolytic streptococci. On June 3 roentgen examination of the thorax revealed evidence of septic pneumonia. On this day the right ear drum was widely incised. At 1 a. m. on June 4 a transfusion of 250 cc. of blood from an immunized donor was given. On June 5 the temperature was 105.2 F. at 4 a. m., 100 F. at noon and 105 F. at 8 p. m. At 10:30 p. m. concentrated streptococcus serum (New York state), 60,000 units (3 ampules), was given intravenously. The response of the patient was gratifying. The temperature remained low for three days, and cultures of the blood, made on June 7 and again on June 10, remained sterile. The right ear drum was again incised on June 10 to promote better drainage, but the patient slowly lost ground; the high fever returned, and a culture of blood taken on June 16 again revealed infection of the blood stream. Two ampules (40,000 units) of the serum were given on June 17. The patient had a rather severe anaphylactic reaction and was given epinephrine by hypodermic injection and later by intravenous injection. On June 19 another intravenous injection of serum (1 ampule) was followed by a severe reaction. Smaller doses (10,000 units) were given on June 24 and June 26. The right ear drum was again incised on June 28, and on the next day an abscess in the neck was incised. The patient was discharged in good condition on July 3.

This patient was not seen by us, but we were consulted by telephone and letter. It would seem that the continuation of serum therapy for several days early in June might have averted the relapse at the middle of the month. The record indicates a favorable effect of the serum and also illustrates the difficulty encountered in starting serum therapy again after an interval of ten or twelve days.

CASE 71.—J. J., a woman aged about 30, the wife of a physician, was seen on Jan. 25, 1936. She had a very red and painful pharynx, mild delirium, a temperature of 104 to 105 F. and a sterile blood culture. Concentrated polyvalent

streptoeoceus serum (Parke, Davis & Co., biological 2005) was given in divided doses to a total amount of 20 cc. The husband reported a severe shock reaction in the evening. On the morning of January 26 the temperature was normal. Small subcutaneous doses (2 cc.) of the serum were continued. Recovery was prompt, and no relapse occurred.

Case 73.—D. B., a woman aged 22, admitted to the hospital Feb. 7, 1936, with pneumonia, empyema and streptoeoceus septicemia, has already been discussed in detail in the preceding paper of this series. Her case is an example of successful use of serum therapy in a desperate situation.

Case 74.—E. M., a woman aged 50, got a bone in her throat on Feb. 12, 1936, and at 2 p. m. on February 13, by operation through the esophagoscope, a bone fragment 25 by 15 by 3 mm. was removed. An esophageal wound about 10 mm. in diameter, below the cricopharyngeus muscle on the right side, resulted in pain, dyspnea, cyanosis and crepitation above the clavicles. A superior mediastinotomy was performed on February 13 at 9 p. m., and rupture of the esophagus was
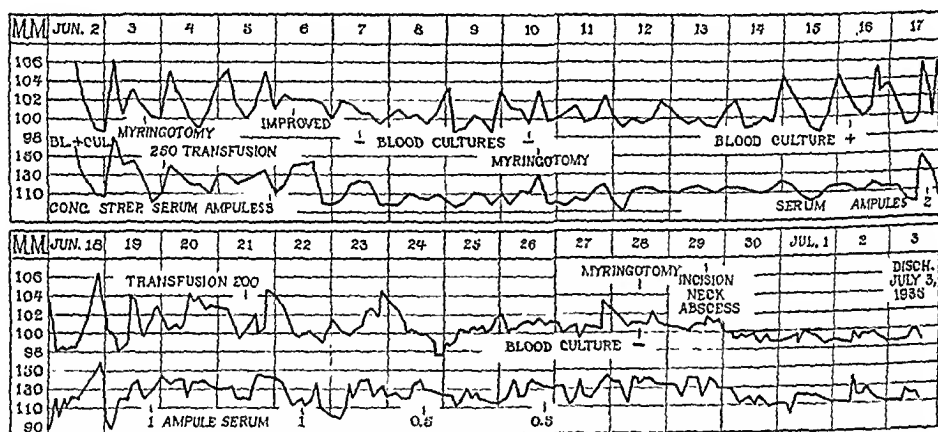
Chart 2 (case 68).—Abridged clinical record of M. M., a girl aged 4 years. This child was admitted to the hospital with a sort throat, otitis media and an abscess on the right side of the neck. Culture of the blood yielded streptococci on the day of admission. She was given a large dose of serum on June 5, to which she responded promptly. Serum was discontinued, however, and the bacteremia returned. On June 17 serum therapy was resumed and continued at forty-eight hour intervals, with a favorable result.

recognized. A feeding tube was passed into the stomach. On February 21 the aid of streptococcus serum was requested by the attending surgeon. Cultures of material from the wound showed predominant hemolytic streptococci. Concentrated polyvalent streptococcus serum (Parke, Davis & Co., biological 2005) was injected into the skin at 11:21 a. m., subcutaneously at 11:26 and 11:41, intramuscularly at 12:12 p. m. and intravenously at 12:42 p. m., 1:39, 2:23, 2:54, and 3:25 p. m., the total amount for the day being 5 cc. of the serum suitably diluted with saline solution for injection. At 4:15 p. m. the patient felt chilly, and the temperature rose to 102.8 F. at 4:30 p. m., falling sharply to 99.4 F. at 12:30 midnight, the lowest temperature since admission. During the next four days there was marked clinical improvement with continued serum therapy, 8 cc. on February 22, 6 cc. on February 23, 6 cc. on February 24, 6 cc. on February 25, 6 cc. on February 26, 4 cc. on February 27, 9 cc. on February 28, 10 cc. on February 29, 10 cc. on March 1.

10 cc. on March 2 and 6 cc. on March 3. The clinical improvement from February 21 to February 25 was followed by a period of unsatisfactory behavior. The temperature rose to 103 F. on February 25. A generalized serum rash appeared on February 29. The temperature reached 104 F. on this day and 104.6 F. on March 1 and March 2. On March 3 an intravenous injection of 4 cc. of serum diluted with 6 cc. of saline solution was given at 9:30 a. m. Five minutes later the patient had a "convulsion" lasting two minutes, during which the pulse was imperceptible. This was followed by a chill which lasted fifty minutes, with a rise in temperature to 106.2 F. at 11:05 a. m. At 11:47 a. m. another intravenous injection of 2 cc. of serum diluted with 8 cc. of saline solution was given, without reaction. Serum therapy was then discontinued. At 4 a. m. on March 4 the temperature was 98. The patient was finally discharged from the hospital on March 27, in good condition.

Case 75.—H. T., a boy aged 14, was admitted to the hospital March 12, 1936, with a temperature of 101.6 F. He had been ill with "tonsillitis and influenza" for two weeks. Roentgen examination at 11 a. m. on March 13 revealed free fluid in the left thoracic cavity, and at 5 p. m. thoracentesis yielded 750 cc. of straw-colored fluid in which hemolytic streptococci were found in pure culture. Examination for tubercle bacilli, including inoculation of a guinea pig, gave negative results. On March 18, streptococcus serum (Parke, Davis & Co., biological 2005) was given, 0.05 cc. of a 1:10 dilution into skin at 1:21 p. m., 1 cc. of a 1:10 dilution subcutaneously at 1:30 p. m., 4 cc. of a 1:10 dilution into muscle at 2:48 p. m. and 10 cc. of a 50 per cent dilution into muscle at 4:55 p. m. The serum was given intravenously on March 19, at 10:42 a. m., 5 cc. of a 1:20 dilution; at 1:48 p. m., 5 cc. of a 1:5 dilution; and at 3:20 p. m., 2 cc. of serum diluted with 3 cc. of saline solution. This patient was not in an alarming condition. The dose of serum was slowly increased to 20 cc. per day, and on March 25, at the onset of serum sickness, the amount of serum was decreased to that which the patient could tolerate, namely 1 cc. of serum per day in three intravenous doses. The dose was reduced to 0.5 cc. per day as the patient improved, and this was continued until his discharge on May 31. Thoracotomy with removal of 5 cm. of the ninth rib was performed on March 31, and on April 28 about 5 cm. of the eighth rib was resected. The total amount of serum used was 157.85 cc. from March 18 to May 31.

After a vacation in the country, this boy returned on August 27 for a tonsillectomy, which was not followed by any complication.

Case 76.—T. L., a woman aged 33, with chronic pulmonary tuberculosis whose sputum contained acid-fast bacilli, had been treated surgically. Pneumothorax was established in June 1935; subsequently pleural adhesions on the left side were severed in December 1935 and again in January 1936. On February 28 thoracotomy was performed. The thin pus obtained yielded a pure culture of hemolytic streptococci. On March 18 the patient was irrational and required oxygen to relieve dyspnea and cyanosis. The temperature reached 104.6 F. The attending physician requested bacteriotherapeutic aid to combat the streptococcus. A culture of blood taken on this date remained sterile. The chest fluid now contained a few gram-negative bacilli in addition to the hemolytic streptococci. Streptococcus serum (Parke, Davis & Co., biological 2005) was given by intracutaneous, subcutaneous, intramuscular and intravenous injection to a total amount of 1.2 cc. on March 18. The divided doses of serum were continued by intravenous injection, 3.5 cc. of serum on March 19, 8 cc. on March 20, 10 cc. on March 21, 22 and 23, 20 cc. on March 24, 10 cc. on March 25 and 26 and 5 cc. on March 27. The purulent exudate

from the pleural cavity now contained relatively few streptococci and abundant gram-negative bacilli. Serum therapy was discontinued. On March 27 an intercostal thoracotomy in the seventh intercostal space at the anterior axillary line was performed, and a drainage tube was inserted in this region. The patient gradually gained in strength and was discharged on July 12, with a persistent sinus. Although she was able to be up and about, the prognosis was unfavorable.

CASE 78.—W. H., a man aged 43, was brought to the hospital by ambulance on March 31, 1936. He had been suffering from a head cold since March 3, otitis media on the right with spontaneous rupture of the ear drum on March 24, moderate fever and swollen, painful joints. A culture of blood taken on March 31 remained sterile. On April 1 the opening in the right ear drum was enlarged by incision. The swelling about the joints continued to increase, and on April 3 both forearms and the left ankle were thought to be purulent. At 5:40 p. m. on April 3, incision of the left ankle and left forearm released purulent exudate in which chains of streptococci were evident on direct microscopic examination. The cultures yielded pure growth of hemolytic streptococci. Without waiting for the result of the culture, serum therapy was started at 6:45 p. m. by intracutaneous, then subcutaneous, then intramuscular and finally intravenous injection, a total of 8.7 cc. of streptococcus serum (Parke, Davis & Co., biological 2005) being used from 6:45 to 8:40 p. m. On April 4 the patient seemed somewhat better. The serum was continued in repeated doses at intervals of twenty to sixty minutes from 9:34 a. m. to 4:20 p. m., the total amount of serum being 23 cc. At 4:55 p. m. the patient had a severe chill lasting thirty minutes, with a rise of temperature to 107.6 F. at 5:35 p. m. There was then profuse diaphoresis which continued until midnight, and the temperature fell to 96.2 F. at 4 a. m. This appears to have been a typical bacteriotherapeutic shock, which we have in the preceding paper designated as the Hugh Young reaction. Intravenous injections of serum were continued every day until the patient was discharged from the hospital on May 16, and he returned for further injections on May 18 and 19. On May 19 he was finally dismissed. Pyemic abscesses in the left thigh, the right leg and the right forearm were incised on April 10. The two cultures of the blood, one made on March 31 and one on April 4, remained sterile. The total amount of serum used was 150.7 cc.

CASE 79.—W. B., a boy aged 8, suffered an attack of measles in March 1936, followed by otitis media and discharge from the left ear since April 5. He was admitted to the hospital on April 17, and mastoidectomy on the left was performed on this day. Culture of material from the mastoid exudate gave a pure growth of hemolytic streptococci. The postoperative progress was unsatisfactory. A transfusion of 350 cc. of blood was given on April 26, and a culture of blood taken on this day remained sterile. On April 27 there was a questionable chill, and the temperature rose to 105.2 F. at 7 p. m. At 7:30 p. m. the left internal jugular vein was ligated, and a clot was removed from the left lateral sinus and jugular bulb. On April 29 there was again a slight chill at 11:40 a. m. Blood was taken for culture, and a transfusion of 250 cc. was given. This was followed by a severe chill lasting twenty-five minutes, with a rise of temperature to 106 F. On the following morning the growth of streptococci was evident in the blood culture of April 29. On April 30 serum therapy was begun with the intracutaneous injection at 9:27 a. m. of serum (Parke, Davis & Co., biological 2005) followed by two subcutaneous injections at intervals of fifteen minutes, two intramuscular injections and four intravenous injections of the same serum, the last one at 11:57 a. m. The total amount of this serum used was 2 cc., and half of this was
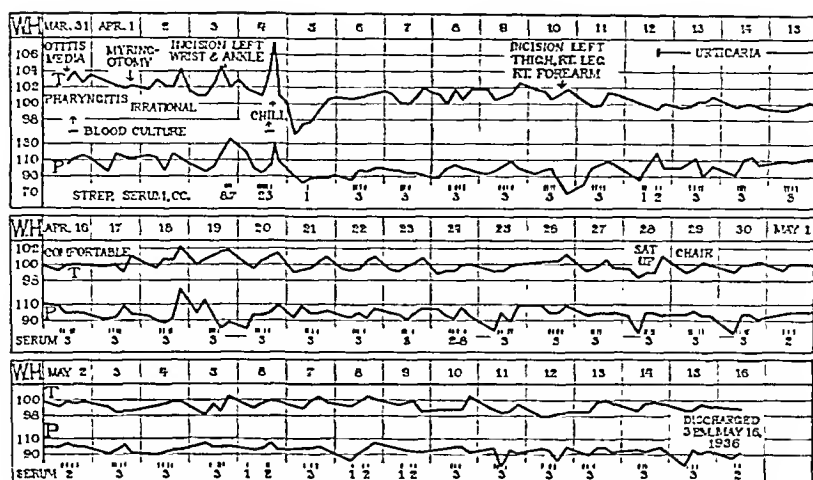
Chart 3 (case 78).—Abridged clinical record of W. H., a man aged 43. In this patient, swollen, painful joints and otitis media with spontaneous rupture of the ear drum had followed a persistent head cold. After pus from the ankle and wrist revealed streptococci, serum therapy was started on April 3. This was continued on April 4, at frequent intervals, to a total of 23 cc., culminating in that typical bacteriotherapeutic shock which we have designated as the Hugh Young Reaction. Serum was continued daily until the patient's discharge, which took place after a fairly uneventful convalescence.
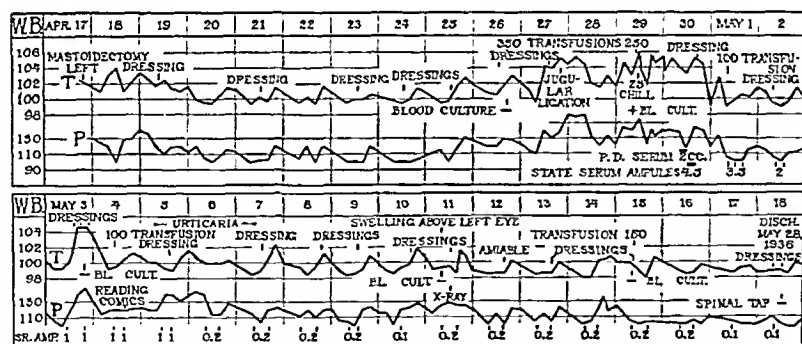
Chart 4 (case 79).—Abridged clinical record of W. B., a boy aged 8. This boy had bacteremia following mastoidectomy and ligation of the left internal jugular vein with the removal of a clot from the left lateral sinus and jugular bulb. Administration of serum on April 30 was followed by prompt improvement. On May 3 the temperature again rose, and there was severe headache. The amount of serum was reduced to one tenth of the previous dose on May 6, and small daily doses were continued through May 18. He was discharged on May 28; complete recovery ensued.

administered by the intravenous route. Beginning at 12:17 p. m. unconcentrated streptococcus serum of the New York state department of health was given intravenously in nine spaced injections, the first one 0.2 cc. and the last one 10.5 cc. at 3:37 p. m., the total amount of this serum being 17.5 cc., or 22,500 units. At 4 p. m. the patient's temperature was 105.2 F. At 5:50 p. m. the wounds were dressed with the patient under nitrogen monoxide oxygen anesthesia administered for fifteen minutes. The patient slept fairly well and perspired freely during the night, and clinical improvement was evident on May 1 and 2. On May 3, however, there was severe headache. A culture of blood taken on this day remained sterile. Subsequently the patient continued to improve slowly, although frequent headaches, paresis of the left facial muscles, a tendency to left internal squint and edema above the left eye suggested continuing inflammatory activity within the cranium. Urticaria of moderate severity was present from May 5 to May 7, and the dose of serum was reduced to one tenth of the previous amount on May 6. Serum therapy was terminated on May 18, and the patient was discharged from the hospital on May 28. Complete recovery followed.

CASE 80.—A. S., a woman aged 45, was admitted to the hospital on April 20, 1936, and on April 24 underwent a partial gastrectomy for diffuse scirrhous carcinoma of the stomach, which could not be completely removed. Four days later pneumonia of the left lung was recognized. As the patient improved from this, severe pharyngitis developed, and on May 4 there was a definite chill. Bacteriologic examination revealed abundant hemolytic streptococci in the throat. Streptococcus serum (Parke, Davis & Co., biological 2005) was injected in small doses from May 6 to May 20, the total amount being 14.54 cc. The pharyngitis was much improved by May 14. The patient was out of bed daily after May 15. She was discharged from the hospital on June 30, in apparently good condition.

CASE 81.—J. W., a man aged 44, was admitted to the hospital April 28, 1936, with chronic nasal sinusitis, acute sore throat and swollen jaw. The abscess of the jaw and a peritonsillar abscess were incised and drained on May 6. At 11:20 a. m. on May 15 the patient had a chill which lasted thirty minutes, and his temperature, which had been below 100 F., rose to 102.2 F. He complained of dyspnea and vomited a large amount of undigested food. A culture of blood taken at this time remained sterile. Spinal tap yielded cloudy fluid containing pus cells and streptococci seen in direct microscopic examination. At 12 midnight mastoidectomy was performed, and on the next day the aid of bacteriotherapeutic measures was urgently requested. Multiple injections of streptococcus serum were given from 12:38 to 3:48 p. m., the total amount being 30 cc. The patient had a severe chill at 4 p. m. which lasted thirty minutes, with a rise in temperature to 106 F. At 6:30 p. m. spinal tap yielded 60 cc. of cloudy fluid, and 20 cc. of the serum was injected into the spinal canal. At 1 a. m. administration of oxygen was started and continued. The patient died at 4 a. m.

CASE 85.—G. P., a man aged 32, a surgeon, was admitted to the hospital at 3:20 a. m., Jan. 12, 1937, with acute maxillary sinusitis complicating a head cold of one week's duration. The patient appeared very toxic. The maxillary sinus was punctured on the morning of January 12. The exudate contained abundant hemolytic streptococci. Sulfanilamide in doses of 20 grains (4 tablets) every six hours was started about 6 p. m. on January 13. At 8 p. m. he was given 1 ounce (30 cc.) of whisky; at 9 p. m. a hypodermic injection of 1/6 grain (0.01 Gm.) of morphine, and at 9:30 1/4 grain (0.015 Gm.) of codeine by mouth. He slept for about two hours. At 12:15 1½ grains of phenobarbital was given, as well

as 30 grains of triple bromides and at 12:45 an eggnog containing ½ ounce of whisky. He was given 20 grains (1.29 Gm.) of sulfanilamide at 1 a. m. At 1:30 a. m. he was sleeping. At 2:35 a. m. (January 14) he awoke in a severe chill which lasted twelve minutes, with a rise in temperature to 102.8 F. After sleeping for another hour he awoke in distress, nauseated, cyanotic and dyspneic. He was also emotionally disturbed. At 4 a. m. the temperature was 104.4 F. The cyanosis became more evident during the forenoon. At a medical consultation at this time it was decided to treat the condition as an infection of the blood stream, and we were requested to see the patient and, after slight delay, to undertake bacteriotherapeutic measures. A culture of the blood was made at 9:40 a. m. on January 14; it remained sterile. Without awaiting the result of this culture the administration of streptococcus serum (Parke, Davis & Co., biological 2005) was begun at 12:25 p. m. by one intracutaneous injection, three subcutaneous injections, three intramuscular injections and two intravenous injections, the last one at 4:42 p. m. The total amount of serum for the day was 5.6 cc. Clinical improvement was evident by midnight. There was marked diaphoresis. At 8:15 a. m. on January 15 the patient awakened smiling. The increasing cyanosis, however, gave considerable concern. The serum was continued by five intravenous injections on January 15 and decreasing amounts thereafter, as shown in the chart. Oxygen administered by funnel on January 15 and 16
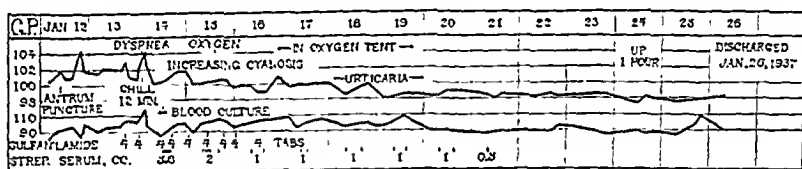
Chart 5 (case *85*).—Abridged clinical record of G. P., a man aged 32. This patient had acute maxillary sinusitis. The pus obtained after puncture of the antrum contained abundant hemolytic streptococci. Sulfanilamide (20 grains) was given the evening of January 13, and serum therapy was instituted on January 14. There was marked improvement on January 15. Sulfanilamide was discontinued on January 16 because of severe cyanosis, but serum was continued through January 21. Recovery was prompt.

seemed to produce no change in the patient's color. Spectroscopic examination of the blood at 10 a. m. disclosed the presence of methemoglobin. Sulfanilamide was discontinued, and the patient was placed in an oxygen tent that afternoon. On January 18 there was marked improvement in color, and the oxygen was discontinued on January 19, after which time progress was uneventful. There was mild urticaria on Jan. 18 and 19. Administration of serum was continued until January 21. The surgical point of view in this case and particularly the cyanosis caused by medication have been discussed elsewhere by Stoness.[3]

CASE 87.—V. B., a man aged 34, who had been in the hospital under treatment for staphylococcic bacteremia, osteomyelitis of the right ilium and carditis with clinical evidence of lesions of the mitral and aortic valves since Oct. 16, 1936, had a running right ear on Jan. 24, 1937. On February 15 a bacteriologic examination of the exudate disclosed a pure culture of hemolytic streptococci. The

3. Stoness, J. F.: Methemoglobinemia and Prontylin, New York State J. Med. **37**:1139-1140 (June 15) 1937.

patient was given sulfanilamide, 5 grains (0.32 Gm.) on February 16, before mastoidectomy, and 5 grains three times a day from February 17 to 25. We also gave him streptococcus serum (Parke, Davis & Co., biological 2005) as follows: 3.25 cc. on February 16, 2 cc. on February 17, 1.4 cc. on February 18, 1 cc. daily from February 19 to February 26 inclusive and 0.5 cc. on February 27 and 28. Mastoidectomy on February 16 was followed by rapid healing of the wound, so that local irrigations were discontinued on March 4 and no further attention to the ear was required. There was a mild serum rash on February 27 and 28. The streptococcic otitis media was merely a minor incident in the prolonged illness of the patient. Part of his clinical record has already been published.[4] He was eventually discharged from the hospital on November 12 and has remained in good condition since.

CASE 88.—E. R., a woman aged 28, attempted to remove wax from the left auditory canal by use of a toothpick on Feb. 17, 1937, and in the evening she noticed two small swellings behind the ear and one in front of the ear. On the next day the swelling extended rapidly to involve the left half of the face. She was admitted to the hospital at 1 p. m. on February 20, at which time the swelling extended from the left mastoid region to the left side of the nose. There was marked edema of the left lower eyelid and of the cheek, particularly about the
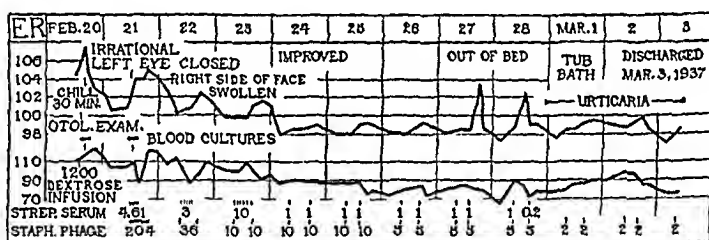
Chart 6 (case 88).—Abridged clinical record of E. R., a woman aged 28. This patient was admitted to the hospital on February 20 with swelling of the left half of the face, extending from the mastoid region to the nose. Edema of the left lower eyelid was noticed. The temperature rose to 107.4 F. after a chill which occurred the same afternoon. Bacteriologic diagnosis was not waited for; the patient was treated for both streptococcus and staphylococcus infections, being given streptococcus serum (Parke, Davis & Company) and also staphylococcus bacteriophage. These agents were both continued as indicated on the chart. Recovery was prompt and uneventful.

opening of Stenson's duct. The temperature was 104.4 F.; the leukocyte count was 18,300, with 95 per cent polymorphonuclears. An intravenous infusion of 1,200 cc. of 5 per cent dextrose solution was given. The results of otologic examination by Dr. Griffith were recorded as follows: "Cellulitis involving auricle with surrounding tissue; middle ear and mastoid normal." Immediately after this the patient had a severe chill lasting from 4:15 to 4:45 p. m., with a rise of temperature to 107.4. Culture of blood taken during the chill remained sterile. On the next day, February 21, the facial swelling had extended to involve the left upper eyelid and forehead, so that the left eye could be opened with difficulty, and had extended to the right side of the face. Marked edema was present about the right eye. The eyeballs appeared normal. Bacteriotherapeutic aid was requested

4. MacNeal, W. J.: The Infectious Organism in Osteomyelitis, J. Bone & Joint Surg. **19**:889-891 (Oct.) 1937.

by the attending surgeon. In the absence of a specific bacteriologic diagnosis it was decided to treat the patient for both streptococcic and staphylococcic infection without further delay. Streptococcus serum (Parke, Davis & Co., biological 2005) was given in divided doses, beginning at 12:10 p. m. by intracutaneous injection, followed by four subcutaneous injections and two intramuscular injections. The last injection was given at 3:40 p. m. The total amount of serum used was 4.61 cc. Staphylococcus bacteriophage was given intravenously in a series of fourteen injections, beginning with 1 cc. at 12:11 p. m. and ending with a dose of 35 cc. at 9:15 p. m., the total amount of bacteriophage being 204 cc. At 6 p. m. the temperature reached 105 F., and the patient complained of feeling cold. There was, however, no frank chill, and at 7:55 p. m. the temperature was still 105 F., falling to 104.6 at 10 p. m. and to 103 at 4 a. m. on February 22. The serum was continued in increasing amount on February 23 and then in small doses to February 28. The bacteriophage was continued in decreasing doses daily to March 3, when the patient was discharged. She has returned twice for immunizing injections and appears to have made a complete recovery. The diagnosis remains somewhat unsatisfactory, but the dissatisfaction in this respect is somewhat ameliorated by the prompt recovery of the patient from an apparently serious disorder.

CASE 89.—K. C., a woman aged 40, admitted to the hospital on April 15, 1937, is one of the most remarkable patients in this entire series. Her record has been reported elsewhere.[5] Here it will suffice to say that the patient received sulfanilamide literally ad nauseam, streptococcus serum in large amounts for eight days and in smaller amounts for thirty-four days more, and streptococcus bacteriophage beginning on the thirteenth day of hospitalization and continuing for thirty-three days. She was discharged in good condition on May 29. She has reported from time to time and was seen again on Feb. 3, 1938, at which time she was in excellent physical condition.

CASE 90.—B. D., a man aged 42, was admitted to the hospital on May 17, 1937, by transfer from another hospital. He had streptococcic bacteremia, apparently originating in otitis media early in April, with complicating pneumonia, pleurisy and suspected endocarditis. He was treated with large amounts of sulfanilamide and streptococcus serum. He died June 13, and necropsy was not permitted. The record of this case has been presented in the preceding paper of this series.

<div align="center">COMMENT</div>

In this series of 30 patients there were 7 deaths. Generalized meningitis with streptococci recognizable in the spinal fluid was present before serum therapy was initiated in 3 of the cases in which fatality occurred, namely cases 33, 50 and 62. We have no evidence to indicate that established diffuse streptococcic meningitis can be controlled by the serum which we have employed. In only 1 instance (case 39), the patient being a boy aged 10 years, was there recovery after definite evidence of meningitis, and in this case, although the spinal fluid was

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5. MacNeal, W. J., and Cavallo, M. E.: Streptococcic Bacteremia and Apparent Thrombosis of the Cavernous Sinuses with Recovery, J. A. M. A. **109**: 2139-2141 (Dec. 25) 1937.

clouded with abundant leukocytes, culture failed to disclose the presence of streptococci in it. The other 4 deaths occurred in patients with streptococcic bacteremia but without meningitis. For the patient in case 53 the serum was used late. The patient in case 56 was given 140,000 units of the concentrated serum (New York state) from March 4 to 14, and then serum therapy was discontinued. Two weeks later bronchopneumonia was recognized; the condition ended in death on April 5. The patient in case 62, aged 5 months, received the concentrated serum (New York state) on May 3, 4 and 5, when a sterile culture of blood was obtained. Smaller doses of unconcentrated serum (New York state) were then given on May 6 and 7. Death occurred on May 8. In this case there seems to have been a frank failure after reasonable use of the serum. The patient in case 90, a man aged 42, was treated with sulfanilamide until May 17 for streptococcic bacteremia originating from otitis media early in April. Streptococcus serum was used from May 17 until death of the patient on June 13. This also is an instance of frank failure of serum therapy after reasonable use. It would be only fair to say that the serum therapy was begun rather late and that there was some indication of vegetative endocarditis which cannot be recorded with confidence in the absence of necropsy.

Among the 23 cases in which the patients survived there were 2 examples of streptococcic otitis media developing in debilitated patients under treatment for staphylococcic osteomyelitis (cases 34 and 87). One of the patients received serum, and the other received serum and sulfanilamide. With both the streptococcic infection proved to be only a minor incident. There were 2 patients with mediastinitis and 1 with streptococcic empyema following pneumothorax for active pulmonary tuberculosis. In all 3 of these the activity of the streptococcus, which threatened to be terminal, was adequately controlled. Two patients had streptococcic pneumonia complicated by voluminous empyema (the patients in cases 73 and 75). One of these, the patient in case 73, responded in an unexpectedly fortunate way, and the other made a good recovery. The patient in case 89, whose case is reported in more detail elsewhere,[5] presented the classic symptoms and signs of septic thrombosis of the cavernous sinuses in the presence of a positive infection of the blood stream with hemolytic streptococci. Sulfanilamide, serum and bacteriophage all were brought into play in this case, with a successful outcome apparently unique in the records. In case 68 the immediate improvement after the first day of serum therapy was so gratifying that the serum was discontinued. Relapse required further serum for its eventual control.

The difficulties and dangers in the use of streptococcus serum are serious and require frequent mention. In a subsequent paper in this

series we hope to consider these in more detail. They are such as to require considerable attention and effort on the part of the physician. On this account we recognize that streptococcus serum will not and probably should not be used for streptococcic infections of moderate severity, which may be adequately controlled by the oral administration of sulfanilamide. When, however, a really grave situation arises in a case of streptococcic infection the proper use of the serum brings a promise of important aid which should not be neglected. Certainly in the all too frequent streptococcic infections of the nose, throat, ear and mastoid the use of sulfanilamide or of serum or of the two in combination may be expected to control the infection and to obviate the necessity of operative procedures. For example, mastoidectomies for streptococcic infection, which formerly constituted about 90 per cent of mastoid operations, will become less frequent when modern chemotherapy and serum therapy for streptococcic infections of the upper part of the respiratory tract and of the middle ear are adequately employed. The success already achieved promises even more for the future development of chemotherapy and specific biotherapy of these infections.

SUMMARY

Thirty patients suffering from severe infection with hemolytic streptococci in the field of otolaryngology, 4 with complicating meningitis and 15 whose blood yielded bacteria on culture, were treated with streptococcus serum of three different kinds, together with other therapeutic measures, including transfusions, sulfanilamide and bacteriophage in certain instances. Seven deaths and 23 survivals occurred.

The early use of serum may be expected to be almost always successful, but because of the effort and expense involved serum therapy will usually be reserved for the more difficult cases.

Advanced and even desperate streptococcic infections may be favorably influenced by the adequate use of streptococcic serum.

The timely exhibition of modern chemotherapeutic and biologic agents for the control of infection with hemolytic streptococci may be expected to reduce appreciably the need for operative procedures for control of such infection and, even after surgical incision, to contribute essentially to reduction of the postoperative mortality and period of convalescence.

SQUAMOUS CELL CARCINOMA OF THE RENAL PELVIS

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CLEVELAND

The occurrence of epithelial tumors of the renal pelvis is rare in comparison with the frequent occurrence of other neoplasms involving the kidney. Joly [1] in reviewing a collected series of 337 cases of tumor of the renal pelvis reported the occurrence of 120 benign papillomas, 138 papillary carcinomas, 29 transitional cell carcinomas and 50 squamous cell carcinomas. In analyzing individual cases it is difficult to classify the tumor accurately, because a varied terminology has been used, as is illustrated by the collected series of nonpapillary tumors of the renal pelvis which Kretschmer [2] studied in 1917. I found that the following terminology had been employed by various authors cited in his collected series. Medullary carcinoma was used by 4 authors; scirrhous carcinoma by 2; pavement epithelium carcinoma by 3; alveolar carcinoma by 3; carcinomatous growth by 2; carcinomatous degeneration by 2; cancer by 3; pavement epithelioma by 9; encephaloid carcinoma by 2; epithelioma by 2; cylindric epithelioma by 1; adenocarcinoma by 1; epidermoid carcinoma by 1; cylindric cell carcinoma by 2; squamous epithelioma by 1; carcinoma-sarcoma by 1, and squamous cell epithelioma by 1. Two authors did not classify the tumor. In some instances a complete microscopic report was not cited, so that correct grouping is impossible.

In 1934, Gilbert and MacMillan [3] reviewed the literature and compiled 55 cases of squamous cell carcinoma of the renal pelvis. They added 2 of their own. Silverstone [4] and Nicholson [5] each reported a

From the Cleveland Clinic.

1. Swift-Joly, J.: Tumors of the Renal Pelvis and Ureter, Brit. J. Urol. 5: 327-328 (Dec.) 1933.

2. Kretschmer, H. L.: Primary Non-Papillary Carcinoma of the Renal Pelvis, J. Urol. 1:405-437 (Aug.) 1917.

3. Gilbert, J. B., and MacMillan, S. F.: Squamous Cell Carcinoma of the Renal Pelvis with Special Reference to Etiology, Ann. Surg. 100:429-444 (Sept.) 1934.

4. Silverstone, M.: Squamous Cell Carcinoma of the Renal Pelvis: Report of a Case, Brit. J. Surg. 24:332-336 (Oct.) 1935.

5. Nicholson, W. F.: Squamous Cell Carcinoma of the Renal Pelvis in a Horseshoe Kidney, Brit. J. Surg. 23:397-399 (Oct.) 1936.

case in the following two years, bringing the total to 59. Five patients
with squamous cell carcinoma of the renal pelvis have been seen at the
Cleveland Clinic. Including these cases, then, the literature now con-
tains 64 reports of squamous cell carcinoma of the renal pelvis.

REPORT OF CASES

CASE 1.—A woman 41 years of age entered the clinic on Aug. 10, 1924. She
complained that for one month she had had chills, fever, profuse sweats and occa-
sional hematuria. Four years prior to this time, three stones had been removed from
the left kidney, and one year previously a mass had been discovered in the right
side. This had grown rapidly and had become increasingly tender. At the beginning
of the onset of the most recent symptoms, two small calculi, which apparently came
from the right kidney, had been passed.

Physical Examination.—Physical examination revealed a large mass in the
region of the right kidney. It was fixed to the adjacent structures and was tender
on palpation.

Laboratory Data.—Examination of the urine showed it to have a specific gravity
of 1.006. Its reaction was alkaline; there was a faint trace of albumin, but no
sugar was present. Microscopically, red blood cells were numerous, and there
were 40 or 50 white blood cells per high power field. Examination of the blood
revealed 3,000,000 red cells and 22,000 white cells per cubic millimeter, with 65
per cent of hemoglobin. The value for urea was 29 mg., and that for sugar
98 mg., per hundred cubic centimeters of blood. When the renal function was
tested with phenolsulfonphthalein there was excretion of 20 per cent at the end
of the first hour and of 25 per cent at the end of the second hour, a total of 45
per cent.

A roentgenogram of the kidneys, the ureters and the bladder showed the
outline of the right kidney to be very large, extending well out and below the
crest of the ilium.

Cystoscopic Examination.—The urine in the bladder was found to be cloudy.
Except for the region around the right ureteral orifice the bladder appeared normal.
In this region there was a nodular "cauliflower" growth the size of a small
walnut, and the ureteral orifice could not be identified. A catheter was passed
to the pelvis of the left kidney, and a test of function was made with phenolsul-
fonphthalein. The dye appeared from the left kidney in three minutes, and the
excretion at the end of one-half hour was 36 per cent. Ten per cent was
collected from the bladder.

Diagnosis.—The diagnosis was carcinoma of the bladder, carcinoma of the
right kidney and ureter and hydronephrosis.

Operation.—Operation was performed August 18, after a blood transfusion.
A great deal of pus was found in the right kidney, and owing to the poor general
condition of the patient the kidney was drained. The temperature and pulse rate
returned to normal in six days, but chills and fever developed, and the patient
died in the hospital twenty-eight days after the operation. Autopsy was limited
to examination of the kidney.

Pathologic Examination.—Grossly the specimen consisted of an enlarged right
kidney which measured 9 by 5 by 5 inches (22.8 by 12.7 by 12.7 cm.). It was
partly firm and was yellowish white, with abundant perirenal fat in which nodules
were palpable. The pelvis of the kidney was dilated and was filled with necrotic

material. On section the surface was yellowish red, and toward the central portion it showed degeneration and hemorrhage. The capsule was thickened; it stripped from the kidney with difficulty, showing portions of tumor growth involving the cortex. At the ureteropelvic junction there was marked thickening, and involvement by tumor growth was noted.

Several sections were taken through different portions of the kidney, and microscopically all showed a similar picture, although in some portions the

Fig. 1 (case 1).—Photomicrograph showing papillary carcinoma of the kidney pelvis.

structure was obscured by degenerative changes. The outstanding features were the large masses and columns of large deeply staining, chromatic stratified epithelial cells which were growing in wild profusion in every direction and infiltrating deeply (fig. 1). Practically no normal renal structure was apparent in any area. Pearl formations were seen in abundance.

The diagnosis was squamous cell carcinoma originating from the right renal pelvis.

CASE 2.—A man 52 years of age was first seen at the clinic on April 14, 1933. His chief complaint was of pain in the back, which had been present for ten weeks. The pain occurred chiefly on the right side and radiated down the right thigh and to the right groin. For two weeks a dull, aching pain had persisted. At the onset of the symptoms hematuria had occurred and had been present at intervals; occasionally clots were passed. Nocturia had been present for one year. During the preceding ten weeks, 10 pounds (4.5 Kg.) in weight had been lost.

Physical Examination.—No abnormality was discovered in the abdomen except muscular spasm over the right lumbar region and tenderness to percussion in

Fig. 2 (case 2).—Bilateral pyelogram showing the left kidney to be normal except for a little rotation on the long axis. The lower calix of the right kidney is normal, but there are compression and infiltration in the upper three quarters of the kidney.

the same area. Slight lordosis was present. The prostate showed enlargement of grade 2; it was firm but not hard or fixed.

Laboratory Data.—Examination of the urine showed the specific gravity to be 1.015. The urine gave an acid reaction; a trace of albumin was present, but there was no sugar. Microscopically there were numerous red blood cells and 15 to 20 white blood cells per high power field. Examination of the blood

revealed 5,490,000 red cells and 10,800 white cells per cubic millimeter; hemoglobin, 87 per cent; neutrophils, 87 per cent; lymphocytes, 8 per cent, and monocytes, 5 per cent. The value for sugar was 110 mg., and that for urea 38 mg., per hundred cubic centimeters of blood. The Wassermann test gave a negative reaction. A roentgenogram of the chest revealed no abnormalities. Roentgen examination of the kidneys, the ureters and the bladder showed no evidence of stones or other pathologic change in the urinary tract.
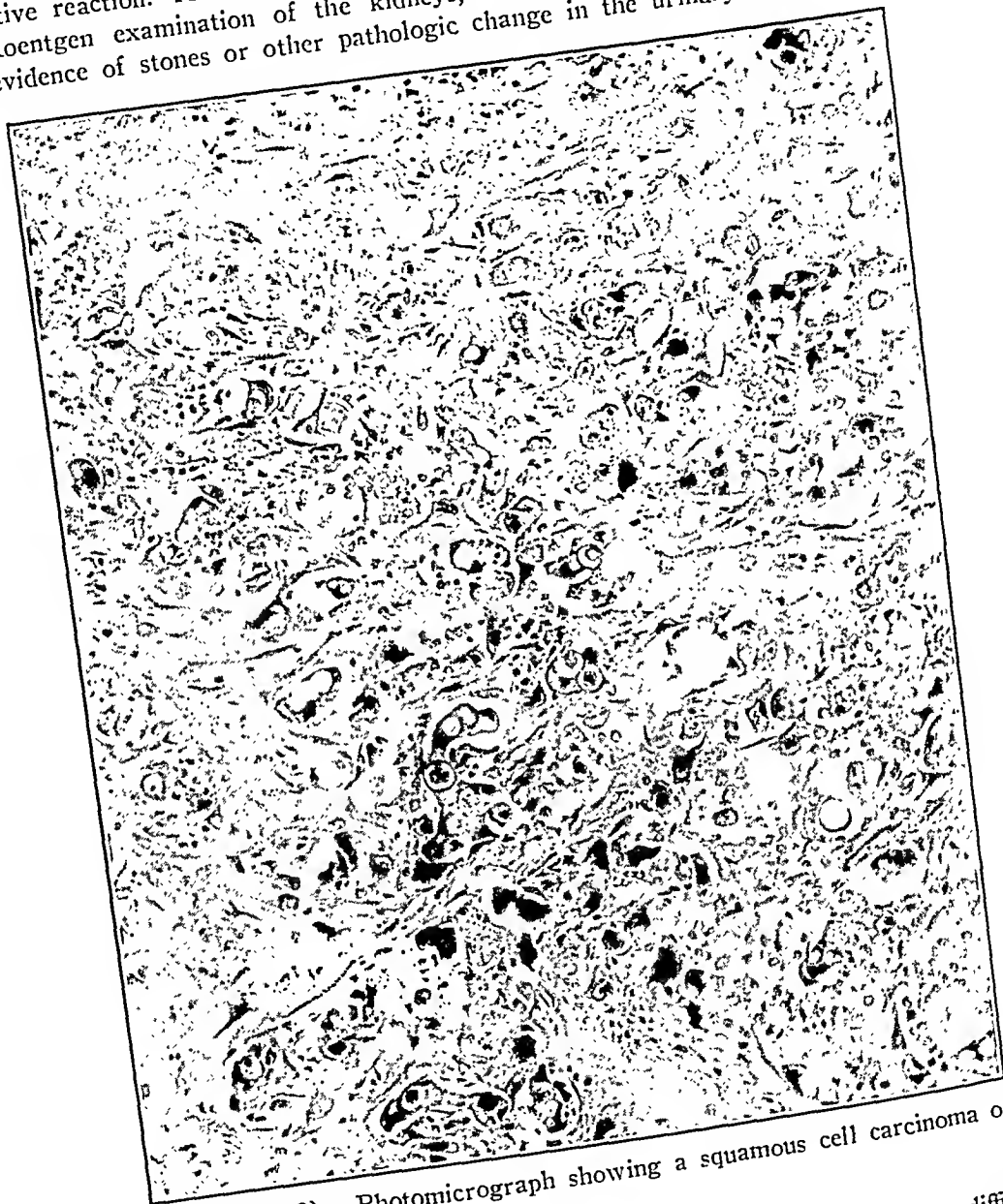
Fig. 3 (case 2).—Photomicrograph showing a squamous cell carcinoma of the kidney pelvis.

Cystoscopic Examination.—The cystoscope was introduced without difficulty. The bladder contained 20 cc. of clear residual urine, and there were no stones, ulcers, tumors or diverticula. Five cubic centimeters of indigo carmine was injected intravenously, and it appeared from the left kidney in four and one-half minutes, with 4 plus concentration, and from the right in six and one-half minutes, with 2 plus concentration. Catheters were passed without obstruction to both pelves, and specimens of urine were secured.

A bilateral pyelogram was made after injection of 7 cc. of solution on the left and 6 cc. on the right. This showed the left kidney to be normal except for a little rotation on the long axis. The lower calix of the right kidney was normal, but compression and infiltration were observed in the upper three quarters of the kidney (fig. 2).

Diagnosis and Treatment.—The diagnosis was carcinoma of the right kidney.

Fig. 4 (case 2).—Photomicrograph showing a blood vessel completely filled with tumor cells.

Roentgen therapy was advised, and six doses at 200 kilovolts, with filtration equivalent to 1 millimeter of copper (1,750 roentgens anteriorly and posteriorly), were given, the kidney receiving about 1,500 roentgens.

Operation.—Nephrectomy on the right was performed on April 28.

Pathologic Examination.—Grossly the specimen consisted of the right kidney and 6 cm. of the ureter. Its weight was 208 Gm. On the anterior surface of the kidney, extending out of the hilus, there was an oval, bulging tumor mass to

which the capsule of the kidney and the perirenal fat were adherent. The tumor measured 7.5 by 6 cm. On section through the kidney a large tumor mass was seen, which had a yellowish gray, moth-eaten appearance. It was not well circumscribed but appeared diffusely infiltrative. The pelvis and calixes appeared somewhat compressed by the tumor mass.

Microscopically, sections through the pelvis of the kidney showed normal pelvic mucosa in some places but complete loss of mucosa in other areas. There were metaplastic changes in the epithelium at other sites. Ulceration of the mucosa and replacement by an infiltrating squamous cell carcinomatous growth were observed (fig. 3). The cells were of the large squamous type, with some tendency to form keratohyaline material but with no pearl formation. The tumor was diffusely infiltrating outward from the renal pelvis into the surrounding medulla, cortex and peripelvic fat. In one section a large branch of the renal artery was intensively infiltrated, and the lumen was occluded by tumor cells (fig. 4). A branch of the renal vein was involved in a similar manner. Throughout the area occupied by the tumor there were atrophy and fibrosis of the kidney tissue.

The pathologic diagnosis was squamous cell carcinoma originating in the pelvis of the right kidney.

Course.—The patient's convalescence was uninterrupted, and he was discharged from the hospital eighteen days after the operation. Roentgen therapy was again instituted.

The patient returned on July 17, two months after discharge from the hospital, complaining of pain in the left side of the chest. Roentgen examination was made, and the following report was given: "The chest shows metastatic malignant changes. There is one rather large nodule in the upper portion of the left lung, as well as nodules in the upper lobe of the right lung."

The patient died from metastases on September 7.

CASE 3.—A man 51 years of age was admitted to the clinic on Dec. 30, 1933, because of pain in the region of the right kidney. He stated that during the preceding three years a dull, aching pain had frequently been present in the right side and was referred to the back and to the right upper quadrant of the abdomen. The periods of discomfort persisted for two or three days and were followed by several weeks of freedom from pain. Blood had been present in the urine at intervals during the last three years. Nocturia (two to three times) had also been noted. One year before this examination the patient had fallen, and at that time a diagnosis of "misplaced kidney" was made.

Physical Examination.—Palpation revealed a large right kidney which was somewhat tender and only partially movable.

Laboratory Data.—The specific gravity of the urine was 1.015; the reaction was acid, and albumin (2 plus) was present. There was no sugar. Microscopically, numerous red blood cells were found, and there were 15 to 20 white blood cells per high power field. The value for urea was 39 mg., and that for sugar 118 mg., per hundred cubic centimeters of blood. A blood count showed 5,290,000 red cells and 10,450 white cells per cubic millimeter; hemoglobin 84 per cent; neutrophils, 84 per cent; eosinophils, 1 per cent; lymphocytes, 12 per cent, and monocytes, 3 per cent. The Wassermann reaction of the blood was negative.

Roentgen examination of the kidneys, the ureters and the bladder revealed huge calcific deposits in the right kidney (fig. 5). This kidney was very large, and a final diagnosis of calculous pyonephrosis was made.

Nephrectomy was performed Jan. 9, 1934, and an enormous kidney containing large and small calculi was removed (fig. 6).

Pathologic Examination.—The specimen was the right kidney. It was received in the laboratory already sectioned. It measured 19.5 by 11 by 5.5 cm. It contained numerous stones and one very large calculus. The capsule was thickened and was adherent to the kidney. On section no normal-appearing cortex or medullary tissue was present. The pelvis and calices were dilated and thickened. At the lower pole, which was the site occupied by the large stone, leukoplakia was present. This was a pearly gray, membrane-like structure which was very
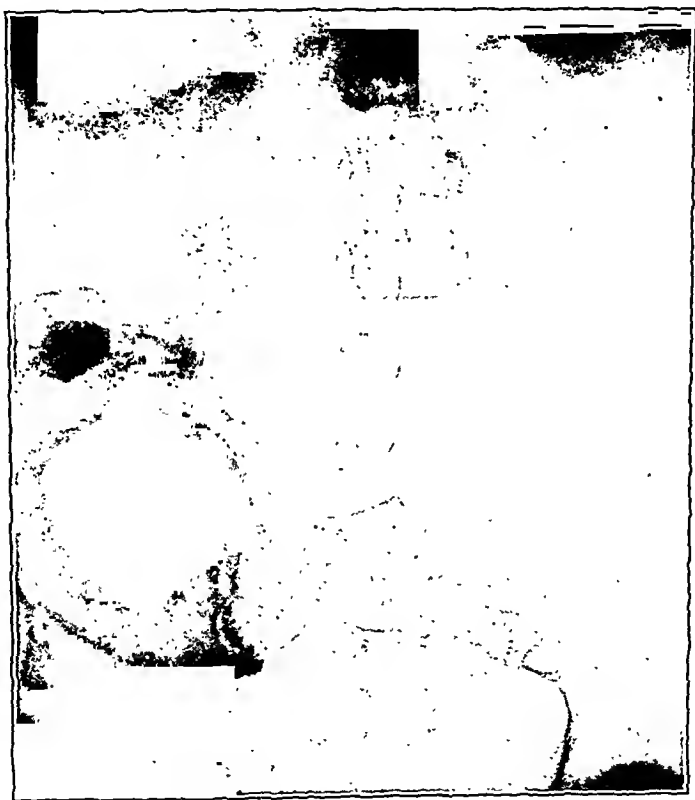
Fig. 5 (case 3).—Roentgenogram showing huge calcific deposits in the right kidney.

adherent. It measured 16 by 9 cm. In a few areas, papillomatous projections of the same structure appeared. There was considerable fibrous thickening in the wall of the pelvis near the ureteropelvic junction and in the septums between the calices.

Microscopically (figs. 7 and 8), sections through the kidney showed atrophy, degeneration, fibrosis and chronic inflammatory changes in the cortex and medulla. There were also ulceration of the pelvic mucosa and diffuse chronic inflammatory infiltration. In several of the sections, small areas and solid nests of rather large epithelial cells were present in the subepithelial layers of the mucosa.

Fig. 6 (case 3).—Kidney after removal, showing large and small calculi.
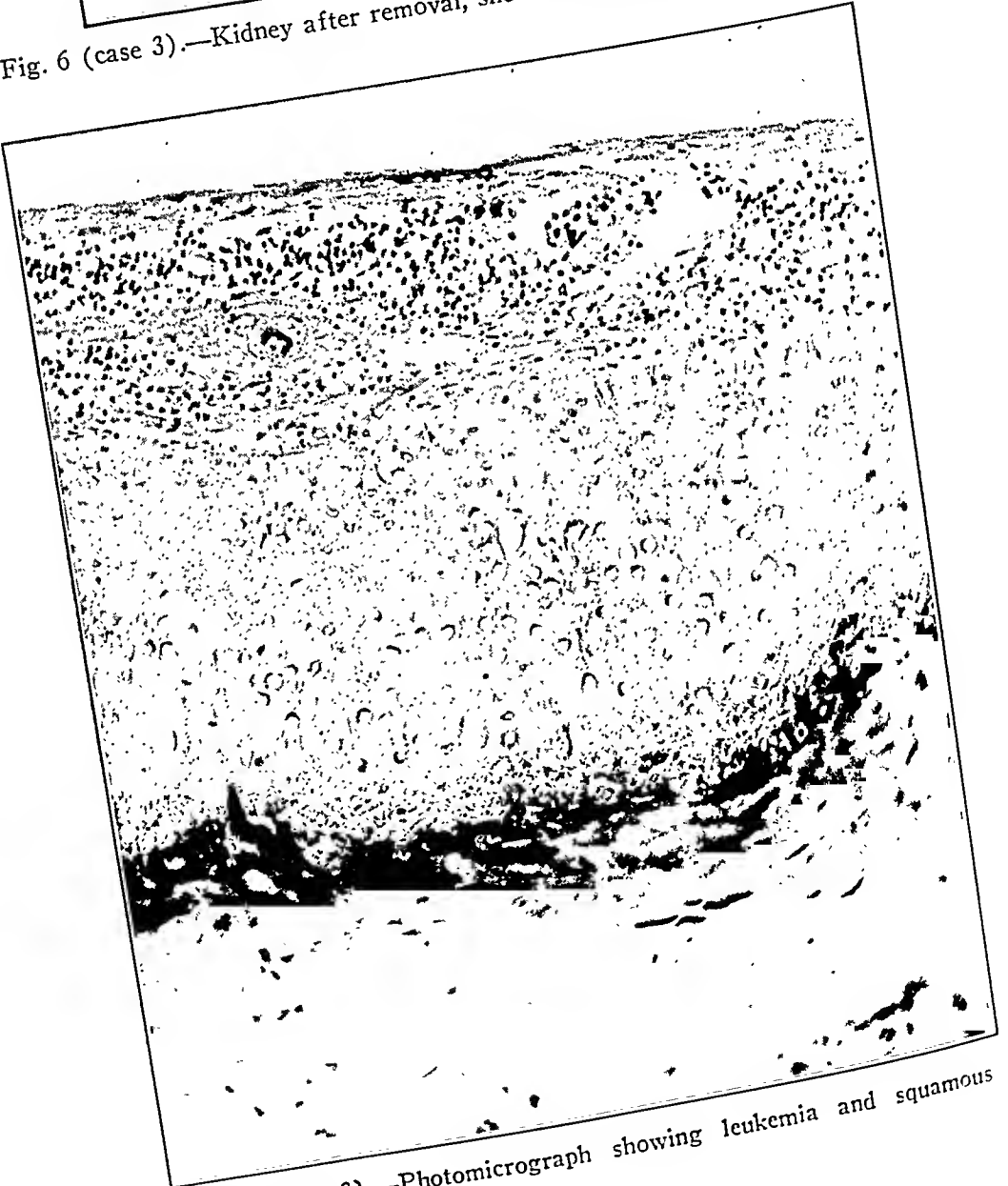
Fig. 7 (case 3).—Photomicrograph showing leukemia and squamous cell carcinoma.

Several sections from the dilated pelvis showed ulceration and chronic inflammation, and in other areas there was complete replacement of the normal epithelium by keratinizing stratified squamous epithelium. There was extensive infiltration of the subepithelial layers of the pelvis by small and large solid masses of stratified squamous epithelium. In some areas the entire pelvic wall was infiltreated, and tumor masses were infiltrating the peripelvic fat.

Fig. 8 (case 3).—Photomicrograph showing a squamous cell carcinoma.

The diagnosis was: nephrolithiasis of the right kidney, leukoplakia, squamous cell carcinoma of the right kidney, pyonephrosis and chronic pyelitis.

Course.—The patient died in the hospital from bronchopneumonia on the twenty-seventh day after the operation.

Postmortem examination revealed bronchopneumonia and also metastases in the perirenal fat, the periaortic nodes and the lungs.

CASE 4.—A woman 49 years of age was first seen by me on June 15, 1932. Her chief complaint was of pain in the left side. Two years before this examina-

Fig. 9 (case 4).—Pyelogram showing a filling defect in the lower calix of the left kidney.
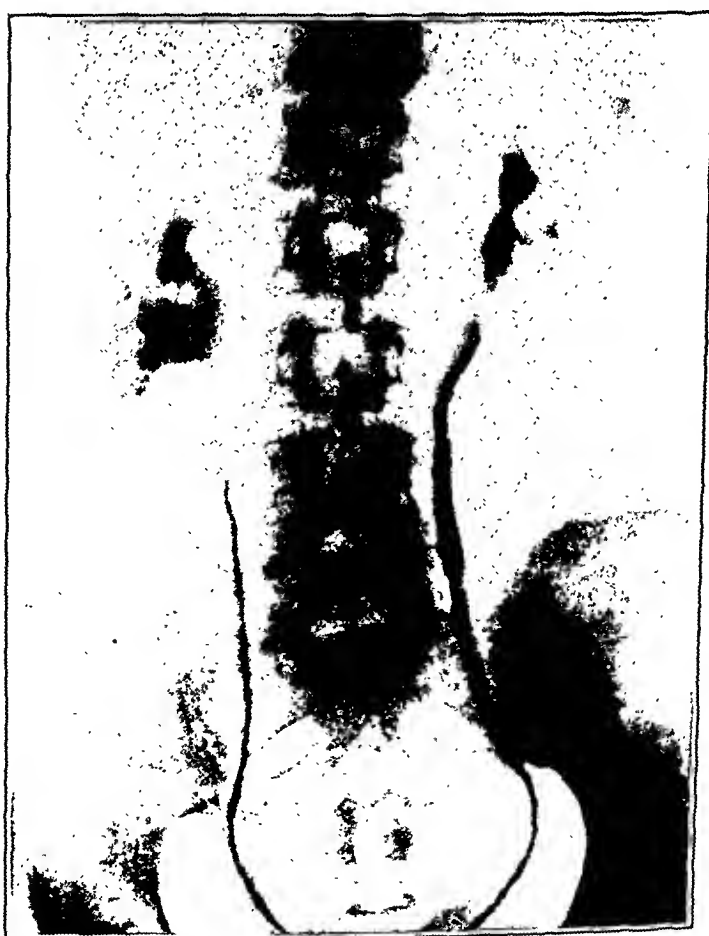
Fig. 10 (case 4).—Pyelogram made eleven months after figure 9, showing a filling defect in the pelvis of the left kidney and narrowing of the ureteropelvic junction.

tion she had had a severe attack of pain in the same side, which lasted for a few hours. Two weeks later a similar attack occurred, after which she was free from symptoms until five months before the present examination. The pains began in the left side of the back and radiated around to the groin and to the upper part of the thigh. They were so severe that morphine was required to relieve them. For five months some pain had been present constantly. After the
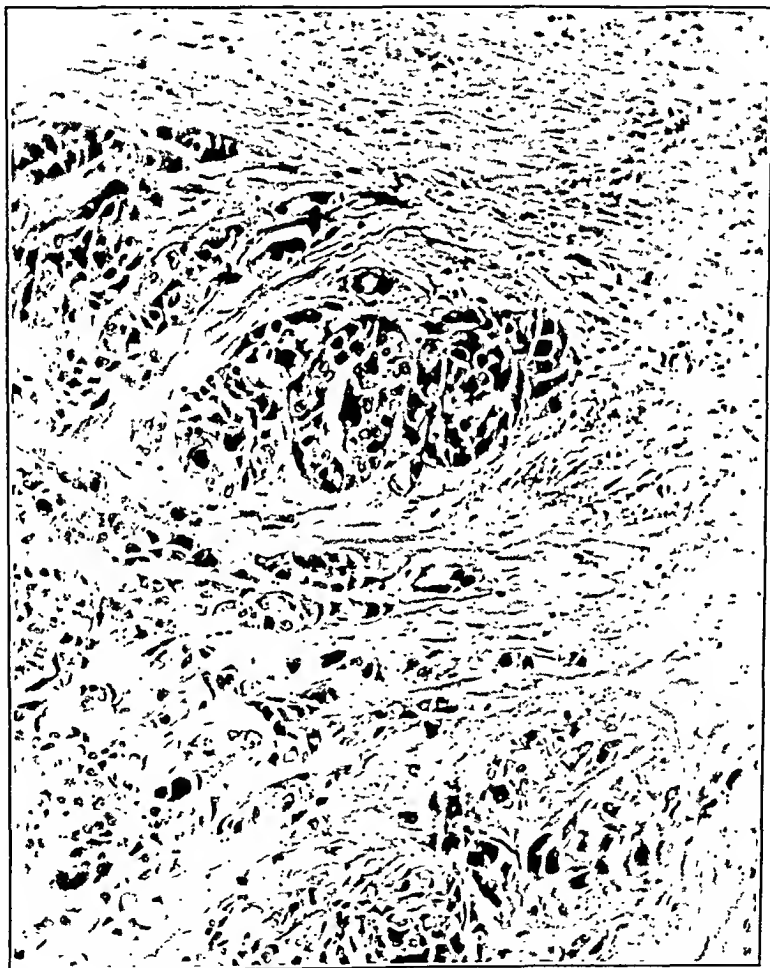
Fig. 11 (case 4).—Photomicrograph showing a papillary carcinoma of the kidney pelvis.

last attack a large amount of blood had been passed, and since that time hematuria had been present for two or three days of each week.

Physical Examination.—No abnormality was revealed, and neither kidney was palpable.

A roentgenogram of the kidneys, the ureters and the bladder showed no abnormality.

Laboratory Data.—The specific gravity of the urine was 1.024; the urine was alkaline. There was a trace of albumin. No sugar was present. Microscopically, 50 to 100 red blood cells and 2 or 3 white blood cells per high power field were found. Examination of the blood showed 5,140,000 red cells and 9,250 white cells per cubic millimeter; hemoglobin 80 per cent; neutrophils, 67 per cent; eosinophils, 1 per cent; lymphocytes, 28 per cent, and monocytes, 4 per cent. The value for sugar was 91 mg., and that for urea 33 mg., per hundred cubic centimeters of blood. The Wassermann reaction of the blood was negative.

Cystoscopic Examination.—The cystoscope was introduced with ease. The capacity of the bladder was 200 cc. The bladder showed no stone, ulcer, tumor or diverticulum. Five cubic centimeters of indigo carmine was injected intravenously and was seen spurting from the ureteral orifices in four and one-half minutes, with a 4 plus concentration. A catheter was passed unobstructed to the left kidney pelvis, and after injection of 8 cc. of solution a pyelogram was taken.

Pyelogram.—The pyelogram showed a filling defect in the lower calix of the left kidney. It was felt that this might be due to incomplete filling, to a blood clot or to tuberculosis (fig. 9).

The patient was advised to await any further development of symptoms. She returned in July 1933, eleven months after the initial examination, and reported that hematuria had been present at intervals. A pyelogram taken at this time showed a filling defect in the pelvis of the left kidney· and narrowing of the ureteropelvic junction, which suggested the presence of a neoplasm (fig. 10). Nephrectomy was advised, and the left kidney was removed June 8, 1935.

Pathologic Examination.—The specimen consisted of the left kidney with 7 cm. of the ureter. It measured 11 cm. longitudinally, 6 cm. transversely and 4.5 cm. anteroposteriorly. The weight of the specimen was 140 Gm. The capsule stripped readily, exposing a smooth, light brown cortical surface in which fetal lobulations were fairly well marked. The lower pole for a distance of 4 cm. was shrunken, atrophic and pale in contrast to the remainder of the kidney. On section this lower portion of the kidney was seen to be largely filled and infiltrated with a hard opaque yellowish white growth measuring 2 cm. on the cut surface. A tumor arose from the pelvis in the region of the lower calix, which it partially filled. The tumor measured 2 by 1 by 1 cm. It was flat and had a broad base. The pelvic mucosa appeared thickened and edematous.

Microscopically (fig. 11), section of the tumor near the ureteropelvic junction showed a somewhat papillary growth of pelvic epithelium, with invasion of the underlying submucosal and peripelvic tissue by large and small solid masses of squamous epithelium showing some keratinization. The tumor cells varied greatly; mitotic figures were scarce. The growth was diffusely infiltrating the medulla of the kidney and extending toward the cortex.

The diagnosis was squamous cell carcinoma of the left kidney pelvis.

Progress.—Convalescence was uneventful. Postoperatively, high voltage roentgen therapy was administered. The patient was last seen June 1, 1936. Her condition was excellent, and there was no evidence of metastasis. This patient is living and well three years after removal of the kidney.

CASE 5.—A man 58 years of age entered the clinic on Nov. 1, 1932, because of pain in the back and blood in the urine. He had been perfectly well until three months prior to his admission to the hospital, when he had had a painless attack of hematuria. Since that time there had been intervals during which the

presence of blood in the urine was not noticed. During the preceding two months he had been aware of a dull, aching pain in the right side of the back and in the thigh. He had lost 30 pounds (13.6 Kg.) in weight in the previous six months.

Physical Examination.—There was a palpable mass in the right upper part of the abdomen; this was firm but movable. Little tenderness was elicited on palpation.

Laboratory Data.—The specific gravity of the urine was 1.007; the urine was alkaline; there was a trace of albumin but no sugar. Microscopically, red blood cells (3 plus) and white blood cells (1 plus) were observed. Examination of the blood showed 4,740,000 red cells and 7,850 white cells per cubic millimeter, with 80 per cent of hemoglobin. A differential count revealed no abnormality. The value for sugar was 102 mg., and that for urea 27 mg., per hundred cubic centimeters of blood. The Wassermann reaction of the blood was negative.

Roentgen examination showed a large mass in the region of the right kidney. The chest was normal, and there was no roentgen evidence of pathologic change in the bony pelves.

Cystoscopic Examination.—The cystoscope was introduced fairly easily. The bladder contained 40 cc. of residual urine. Both ureteral orifices were seen, and the catheters were passed without obstruction to both kidney pelves. No secretion was demonstrable from the right kidney. After the injection of 7 cc. of solution on the left side and 5 cc. on the right side a bilateral pyelogram was taken.

The pyelogram revealed a tumor of the right kidney.

An intravenous urogram did not give findings satisfactory for diagnosis.

The final diagnosis was tumor of the right kidney.

A nephrectomy on the right side was performed with some difficulty on November 12. A plug of tumor was present in the renal vein; however, a pedicle clamp could be placed below the involved portion of the vein. This tore an opening in the vena cava, which was sutured, and a blood transfusion was administered at the completion of the operation.

Pathologic Examination.—The kidney measured 9.5 by 6 by 5 cm. It was firm, and the capsule stripped with some difficulty, exposing a smooth yellowish brown cortex. Section through the kidney showed a moderately dilated pelvis, the mucosa of which was rather rough and had a moth-eaten appearance and from which there were numerous small papillary projections. The peripelvic fat was hard and fibrous and was apparently infiltrated with tumor tissue. At the hilus of the kidney the peripelvic fat, the ureter and the blood vessels were all involved, and a small probe was passed through the ureteropelvic junction with difficulty.

Microscopically, sections through the kidney, including the pelvis, showed a thickened pelvic surface covered by single and multiple layers of rather large, atypical epithelial cells having an epidermoid appearance but showing no keratinization. Extending upward and outward from the pelvis were small and large solid masses of similar epithelial cells diffusely infiltrating the medullar cortex and the capsule proper of the kidney. Section of the fatty extrarenal tissue showed diffuse infiltration by small masses of large epithelial cells similar to those which have been mentioned.

The diagnosis was squamous cell carcinoma of the renal pelvis.

Course.—Convalescence from the operative procedure was uneventful, but a metastatic lesion of the upper end of the left femur was found on December 16, and the patient died three years later.

ETIOLOGY

The relation between leukoplakia and squamous cell carcinoma of the renal pelvis is frequently cited in the literature. In 1929, Kutzmann[6] reviewed 67 cases of leukoplakia of the renal pelvis and concluded that this condition might be a forerunner of squamous cell carcinoma. A coincidental involvement of the renal pelvis occurred in 11.9 per cent of his cases. Patch[7] collected 12 cases from the literature and added 1 of his own, in which he demonstrated the transitional stages between leukoplakia and squamous cell carcinoma. He felt that such a condition is definitely precancerous and that his findings offered evidence in favor of a transitional stage between leukoplakia and squamous cell carcinoma. Cabot's[8] findings seem to confirm the relation between these two pathologic entities. For his patient a suprapubic cystotomy was performed, and a thick sheet of pearly tissue was removed from the vesical wall. A diagnosis of leukoplakia or pachyderma vesicae was made. Pavement epithelial cells were found in the bladder washings. Eight years later the patient returned, and a fistula was found above the pubis. The bladder was explored, and a portion which was removed showed squamous cell carcinoma.

In the case reported by Hinman and his associates,[9] sections of the renal pelvis showed definite leukoplakia; however, in some sections atypical epithelial cells were present, and the leukoplakic areas in certain sites showed a papillary downgrowth with a beginning break in the basement membrane. He stated that the microscopic picture closely resembled that of carcinoma and that such a condition should be considered precancerous.

The striking relation between renal calculi and squamous cell carcinoma has been noted by many observers. It is believed by some authors that the development of metaplastic changes may be induced by long-continued irritation from chronic inflammation or from renal calculi. This seems especially probable since a review of a number of case reports shows that the presence of calculi or of chronic inflammation of the renal pelvis seems definitely to antedate the malignant lesion.

Hallé[10] stated that chronic inflammation or the presence of calculi may initiate an epithelial change in the mucosa of the urinary tract

6. Kutzmann, A. A.: Leukoplakia of the Renal Pelvis, Arch. Surg. **19**:871-897 (Nov.) 1929.

7. Patch, F. S.: The Association Between Leukoplakia and Squamous Cell Carcinoma in the Upper Urinary Tract, New England J. Med. **200**:423-437 (Feb. 28) 1929.

8. Cabot, cited by Patch.[7]

9. Hinman, F.; Gibson, T. E., and Kutzmann, A.: Leukoplakia of the Kidney Pelvis, Surg., Gynec. & Obst. **39**:472-489 (Oct.) 1924.

10. Hallé, cited by Kretschmer.[2]

and that the normal epithelium becomes transformed into stratified squamous epithelium with epidermoid characteristics. Thus the presence of a squamous cell carcinoma of the renal pelvis, which under normal conditions does not contain squamous epithelium, may be explained by metaplasia of the normal epithelium to stratified squamous epithelium and the formation of leukoplakia, which in some instances may undergo a carcinomatous change in certain areas. Albarran [11] expressed the opinion that chronic irritation by calculi may be conducive to the formation of leukoplakia and that the latter may be the first stage in the development of squamous cell carcinoma. The relation between leukoplakia and the subsequent development of carcinoma in other parts of the body is frequently mentioned.

It is also of interest to note that epithelial changes may occur in the presence of vitamin A deficiency, as reported by Wolbach [12] and as I noted during my experimental work on the formation of urinary calculi in white rats.[13] Wolbach stated:

> In vitamin A deficiency, in the human called xerophthalmia or keratomalacia, we found in rats and guinea pigs a very striking and extensively distributed metaplasia of epithelium in the conjunctivae, the ocular glands, alimentary tract, respiratory tract, and genito-urinary tract. In these locations, the epithelium becomes replaced by a stratified, keratinizing epithelium, a condition similar to or comparable with leukoplakia.

In analyzing clinical cases, however, one finds that renal calculi, long-continued chronic inflammation and leukoplakia are the predominating precursors of squamous cell carcinoma of the renal pelvis.

FREQUENCY

Fifty-nine cases of squamous cell carcinoma of the pelvis of the kidney have previously been reported in the literature. McKenzie and Ratner [14] have stated that tumors of the renal pelvis comprise from 5 to 7 per cent of all renal tumors. Kretschmer,[2] in reviewing 43 cases of nonpapillary tumors of the renal pelvis, noted the presence of epidermoid structure in 17 instances. In a series of 35 renal tumors reported by Bowen and Bennett,[15] 5 squamous cell carcinomas were

11. Albarran, J.: ˙Neoplasmes primitifs du bassinet et de l'urétère, Ann. d. mal. d. org. génito-urin. **18**:701, 1918 and 1179, 1900.

12. Wolbach, S. B., in discussion on Patch.⁷

13. Higgins, C. C.: Experimental Production of Urinary Calculi, J. Urol. **29**: 157-170 (Feb.) 1933.

14. McKenzie, D. W., and Ratner, M.: Tumors of the Renal Pelvis: Review of the Literature and Report of a Case, J. Urol. **28**:405-418 (Oct.) 1932.

15. Bowen, J. A., and Bennett, G. A.: Squamous Cell Carcinoma of the Kidney Pelvis, J. Urol. **24**:495-501 (Nov.) 1930.

found microscopically. Patch [7] collected a series of ·152 cases of squamous cell carcinoma of the kidneys, the ureters and the bladder. Jocelyn Swan [16] in 1933, in a personal series of 65 cases of renal tumor, noted 2 lesions which were classified as squamous epithelioma.

Since the review of the literature by Gilbert and MacMillan [3] in 1934, a case has been reported by Silverstone [4] in 1935, and in 1936 Nicholson [5] reported the occurrence of a squamous cell carcinoma involving a horseshoe kidney. This, with my series of five squamous cell tumors, makes a total of 64 cases.

AGE

In the majority of reported cases the lesions have occurred in patients in the fifth decade of life, the average age being 56 years. In the Cleveland Clinic series the ages were 41, 52, 51, 49 and 58 years, respectively. Silverstone [4] stated that 50 per cent of the lesions occur in patients between the ages of 40 and 60. One patient cited by Kischensky [17] was 32 years of age, while Simpson [18] reported the case of a patient who was 79.

SEX

In the cases reported the tumors have occurred in 36 male and 28 female patients. Gilbert and MacMillan, in reviewing 57 cases, found that the tumor occurred in 31 males and 26 females. This is in contrast to some reports in the literature, in which it is stated that the tumor occurs twice as frequently in the male sex. In this series there were 3 female and 2 male patients.

KIDNEY INVOLVED

Gilbert and MacMillan [3] stated that from the data available in their cases 26 lesions involved the right and 26 the left kidney. The right kidney contained the tumor in the case reported by Silverstone, [4] while the tumor reported by Nicholson [5] occurred in a horseshoe kidney. In this series, the right kidney contained the tumor in 4 instances and the left kidney in 1.

SYMPTOMS

No definite symptoms are pathognomonic of squamous cell carcinoma of the renal pelvis. In many cases reported in the literature the symptoms have been referable to a coexisting renal calculus. Some observers

16. Swan, R. H. J.: New Growths of Kidney, with an Analysis of Sixty-Five Cases, Brit. M. J. 1:606-610 (April 8) 1933.

17. Kischensky, D. P., cited by Gilbert.[3]

18. Simpson, C. M.: Malignant Tumors of the Renal Pelvis, Texas State J. Med. 26:787-791 (March) 1931.

have stated that hematuria rarely occurs in association with this type of tumor, owing to its relative avascularity in comparison with papillary tumors; however, this symptom was present in each of my 5 patients. Kretschmer [2] stated that hematuria is one of the most important symptoms of tumor of the renal pelvis and that it may be the only symptom. Usually the bleeding is not accompanied by pain.

Each of my patients complained of symptoms referable to pyuria, which was due either to a calculus or to chronic inflammation, and of pain in the back. The latter symptom has been present in 43 per cent of cases in the collected series.

Loss of weight is a late manifestation, usually occurring after metastases have developed. Scholl [19] has stated that the condition may produce no symptoms and that when obstruction at the ureteropelvic junction occurs it is from slow occlusion, which at times causes enormous dilatation of the renal pelvis but little pain.

<div style="text-align:center">DIAGNOSIS</div>

Early diagnosis is essential; however, this may be difficult even when all available facilities are employed. Squamous cell carcinoma must be differentiated from tumor involving the renal parenchyma, from non-opaque calculi in the renal pelvis and from renal tuberculosis in an early stage.

The presence of a palpable mass may direct attention to the possibility of a renal tumor, such as occurred in 1 of my patients. Owing to the development of hydronephrosis, as Scholl has stated, the mass may attain considerable size. The initial roentgenogram may reveal enlargement of the kidney, thus indicating the need for cystoscopic investigation and pyelography.

Pyelography is the most important means of establishing a diagnosis. A persistent filling defect in the renal calix must be differentiated from early renal tuberculosis, as was considered in 1 of my cases. Here a clinical history of irritability of the bladder and the cystoscopic findings are of value in ruling out renal tuberculosis. Examination of the urine for tubercle bacilli and also inoculation of guinea pigs may be of value. Occasionally the presence of a calculus may mask the true condition, and the malignant tumor may be found only after examination of the specimen which has been removed. A pneumopyelogram or variation in the concentration of the pyelographic medium may be of value in determining the presence of a nonopaque calculus. In the majority of cases, a tumor primary in the renal parenchyma will present pyelographic evidence that the lesion is not primary in the renal pelvis.

19. Scholl, A. J.: Squamous Cell Tumors of the Kidney Associated with Stone. J. A. M. A. **100**:236-238 (Jan. 28) 1933.

Tests of renal function obviously are of value in ascertaining the function not only of the kidney containing the tumor but also of the opposite kidney.

COEXISTING PATHOLOGIC CONDITIONS

Leukoplakia and renal calculi are the two conditions most frequently associated with squamous cell carcinoma of the renal pelvis. A chronic inflammatory process often is present. Darmady,[20] Wells,[21] Scholl,[19] Menetrier and Martinez,[22] Kretschmer,[23] Patch,[7] Hinman[9] and others have discussed such coexisting pathologic conditions. Bugbee[24] cited a case in which the tumor was associated with an impacted ureteral calculus. It is stated that renal calculi are found in the presence of squamous cell carcinoma of the kidney pelvis in approximately 52 per cent of cases. Hydronephrosis and pyonephrosis have been present in many instances. This was due to obstruction at the ureteropelvic junction, which was produced by involvement by the malignant growth or by a calculus in the renal pelvis. Squamous cell carcinoma has been reported as occurring in horseshoe kidneys in 4 instances, by Primrose,[25] Willan,[26] Melen and Gasper,[27] and Nicholson.[5]

PATHOLOGIC PICTURE

Two types of lesion predominate. In the first type the tumor cells invade the renal parenchyma early and eventually replace it. Silverstone[4] stated that as the growth progresses to the periphery the epithelium becomes more anaplastic, more rapidly growing and more primitive, so that it resembles carcinoma simplex. He stated that this type is most frequently associated with calculi. Such findings were not noticed in the pathologic specimens in this series.

20. Darmady, E. M., cited by Scholl.[19]

21. Wells, H. G.: Carcinoma of the Kidney as a Sequel of Calculi, Arch. Surg. 5:356-365 (Sept.) 1922.

22. Menetrier, M. P., and Martinez, M.: Lithiase et cancer du rein, Bull. Acad. de méd., Paris 79:65-74 (Jan. 22) 1918.

23. Kretschmer, H. L.: Leukoplakia of the Kidney Pelvis, Arch. Surg. 5:348-355 (Sept.) 1922.

24. Bugbee, H.: Primary Carcinoma of Kidney with Impacted Ureteral Calculus, J. Urol. 5:267-278 (April) 1921.

25. Primrose, A.: Squamous Cell Carcinoma of the Kidney: Report of a Case Occurring in a Horseshoe Kidney Complicated by Calculus Pyonephrosis, J. A. M. A. 75:12-16 (July 3) 1920.

26. Willan, R. J.: Giant Renal Calculus with Epithelioma in a Horseshoe Kidney, Brit. J. Surg. 16:317-321 (Oct.) 1928.

27. Melen, D. R., and Gasper, I.: Calculus Pyonephrosis in Carcinomatous Horseshoe Kidney, J. Urol. 25:43-52 (Jan.) 1931.

The second type of lesion is confined chiefly to the renal pelvis. This is covered by a tumor mass which in some areas has a papillary appearance. With this type, involvement of the ureteropelvic junction occurs earlier, and extensive hydronephrosis with atrophy of the renal parenchyma is found.

Metastases.—Metastases are stated to occur early and are widespread, dissemination through the blood stream being evidenced by lesions in the lungs, the liver and the bones. Metastases also invade local lymphatic glands. However, in many instances a diagnosis is not established early and the carcinoma has extended beyond the confines of the kidney when first recognized. As in many instances calculi and leukoplakia coexist with or precede the malignant process, the carcinoma is undoubtedly present for a long period but is not suspected.

In 19 autopsy studies cited by Kretschmer,[2] the liver was found to be involved in 8 instances, the peritoneum in 3, the lungs and pleura in 5, the bones in 5 and other organs in isolated cases. In this series, metastasis to the lungs occurred in 1 case. In the second case the perirenal fat, the periaortic lymph nodes and the lungs were involved. In the third case an autopsy of the entire body was not done; in the fourth case there was no evidence of metastasis, and in the fifth case metastasis to the upper end of the femur occurred.

TREATMENT

Early diagnosis followed by nephrectomy is the procedure of choice. In this series, in which preoperative high voltage roentgen therapy was employed, there was no evidence of a reduction in the size of the tumor. Postoperative roentgen therapy is advisable. Diagnosis is frequently not established until late in the course of the disease, and metastases may be present when the patient first consults the physician.

PROGNOSIS AND END RESULTS

The prognosis is grave, owing to the frequency of metastasis. In a review of the literature I was unable to find the report of a patient who was free from metastases at the end of five years. In 5 of the cases reviewed by Scholl,[10] 4 patients died during the first four months after operation, and 1 was living six months after operation. Kretschmer[2] reported that the immediate mortality was high for nonpapillary tumors of the renal pelvis. Of 30 patients on whom operation was performed, 16 died immediately or soon after operation, the operative mortality of the series being 53.3 per cent.

The average duration of life was seven months and fifteen days. In this series 1 patient died from bronchopneumonia twenty-eight days

after operation. The second died five months after operation with metastases in the lungs; the third died from generalized metastases one month after operation. The fourth patient is living and well three years and eight months after operation, with no evidence of metastasis, and the fifth patient died of metastases two years and nine months after operation.

CONCLUSIONS

1. Squamous cell carcinoma of the renal pelvis is relatively rare.

2. Diagnosis is not established early, and metastases are frequently present when the patient is first seen by the physician.

3. The prognosis is grave.

4. The importance of complete urologic investigation in cases of hematuria is well demonstrated by a study of this series of tumors.

GROWTH IN LENGTH OF THE VERTEBRAE

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Growth in length of the long bones in man and animals is caused by a purposeful multiplication of cartilage cells of the epiphysial cartilage plates. It is held that in the vertebrae of man the center grows within itself until it occupies the entire cartilaginous area free to it and there is not the characteristic columnar formation of cartilage cells. The epiphysis is therefore not a growth body but an organ of fixation concerned with the architecture of the spine. It is even claimed that in animals, in spite of the fact that the epiphysis is a complete disk, it does not share in the process of longitudinal growth.

The importance of this problem warranted further study of the growth of the vertebrae of animals. On gross examination of a vertebra of a dog a cartilage plate is found at each end. The microscopic appearance of this plate is similar in structure to the epiphysial plate of any long bone (fig. 1).

In order to determine whether growth takes place at the epiphysial cartilage plate a series of experiments were performed, in which markers were placed in the bodies and in the epiphyses of the vertebrae. If the markers in the epiphysis and those in the body of a vertebra separated, it would show that the epiphysial plate was functioning to increase length. If the markers in the body did not separate, it would indicate that there was no interstitial growth.

The following experiments were performed on dogs under ether anesthesia.

Dog 1 (aged 2 months).—On Nov. 5, 1937, through an abdominal incision, the bodies of the second and third lumbar vertebrae were exposed. After identification of the epiphysial plate a silver wire marker was inserted into the body of the second lumbar vertebra. Into the third lumbar vertebra four markers were placed in different parts. One was placed in the lower epiphysis and three in the body (fig. 2).

A roentgenogram (fig. 3) taken one hundred and twelve days later (February 25) showed the markers in the body of the fourth lumbar vertebra to be the same distance apart and in the same relative position as at the time of insertion. The marker in the lower epiphysis of the fourth lumbar vertebra had separated from these three, owing to growth at the intervening epiphysial cartilage plate. The marker in the body of the third lumbar vertebra had separated a greater distance because of the growth of the lower epiphysial plate of the second and the upper plate of the third lumbar vertebrae.
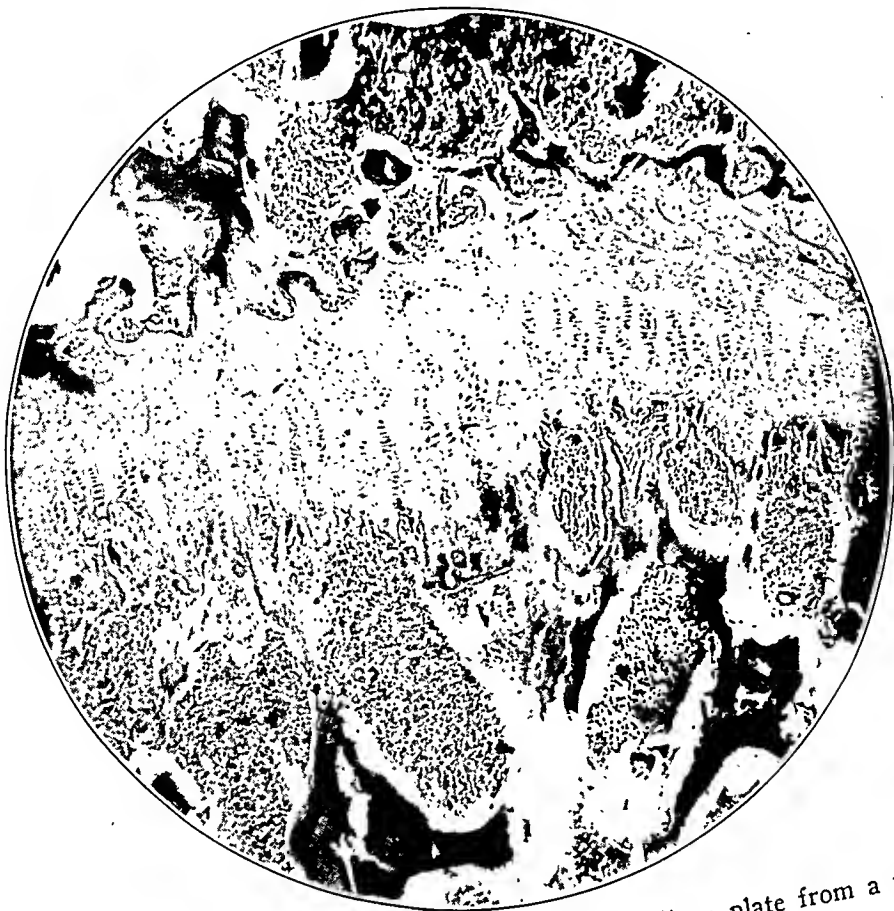
Fig. 1.—Photomicrograph of the epiphysial cartilage plate from a vertebra of a dog 2 months old.
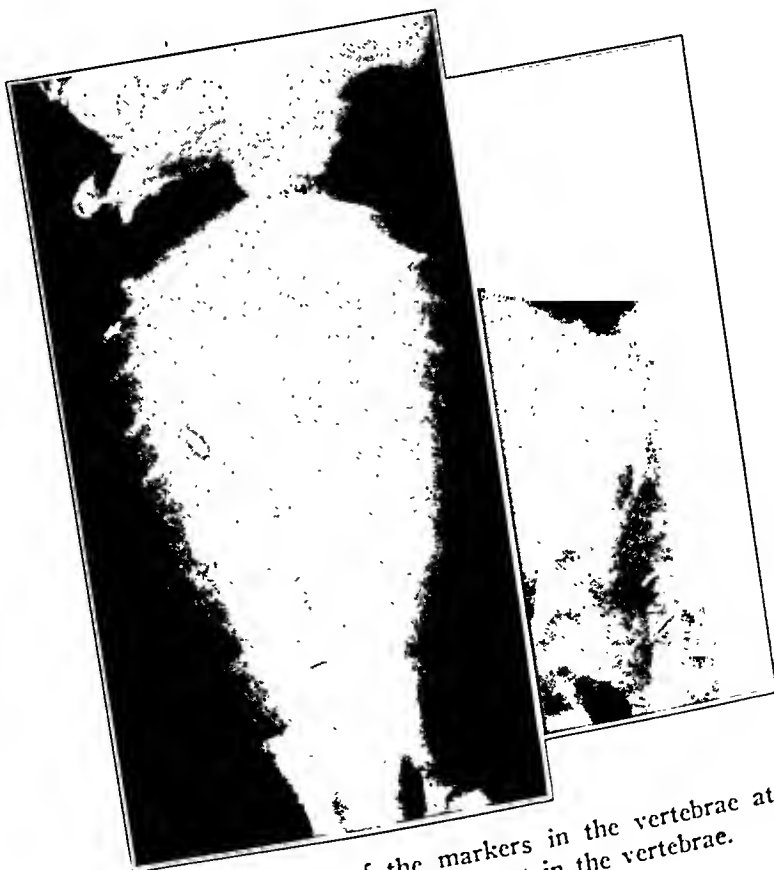
Fig. 2 (dog 1).—Position of the markers in the vertebrae at the beginning of the experiment. The lowest marker is not in the vertebrae.

Fig. 3 (dog 1).—Position of the markers one hundred and twelve days after insertion. Note that the markers in the vertebral bodies have not separated from each other, while those in the epiphyses have separated from those in the bodies. Compare with figure 2.

Fig. 4 (dog 2).—Position of the markers in the vertebral bodies at the beginning of the experiment.

Dog 2 (aged 2 months).—On Nov. 5, 1937, through an abdominal incision, the fourth and fifth lumbar vertebrae were exposed. Three markers were placed in the fourth, two in the body and one in the lower epiphysis. In the fourth lumbar vertebra a marker was placed in each epiphysis and two in the body (fig. 4).

The roentgenogram (fig. 5), taken one hundred and twelve days later (February 25) showed no change in the position of the markers in the body of the fourth lumbar vertebra but a separation of the markers in the epiphysis caused by growth of the intervening epiphysial cartilage plate. In the fifth lumbar vertebra the

Fig. 5 (dog 2).—Roentgenogram taken one hundred and twelve days after insertion of the markers. The markers in the vertebral bodies occupy the same position. The markers in the epiphyses have separated from those of the bodies, owing to growth at the epiphysial plates. Compare with figure 4.

two markers in the body were in the same position, but the markers in the upper and lower epiphyses had separated from those in the body, owing to the growth at the intervening epiphysial plates.

COMMENT

The results of these experiments on dogs show that growth in length of the vertebrae occurs in a manner similar to that of growth in length of the long bones, namely, by proliferation at the epiphysial cartilage plate.

There is no interstitial growth in the body of the vertebrae, as the markers placed in the bodies remained in the same relative positions as at the time of insertion. In the vertebrae of the dog the epiphysial cartilage plate is the growth body, but it is held that in man there is no such structure. Further study may give some clue as to the exact mechanism in man and may help to explain this single point of difference in osseous growth in man and in experimental animals. It is possible that some other interpretation of the findings in man may allow a correlation of the process with that of the lower animals.

CONCLUSIONS

1. The vertebrae of the dog increase in length as do the long bones, i. e., by a purposeful multiplication of the column of cells at the epiphysial cartilage plate.

2. There is no interstitial growth in the bodies of the vertebrae.

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POSTERIOR DISLOCATION OF LOWER FEMORAL EPIPHYSIS IN BREECH DELIVERY

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Hartshorn [1] said that traumatic periostitis might follow breech delivery. Snedecor, Knapp and Wilson [2] reported an occurrence of traumatic ossifying periostitis after such a delivery. They reported 4 cases, the major symptoms in which were pain, swelling, limitation of motion and discoloration of the affected part. The humerus and the femur were the bones involved. Diagnosis was made late, by means of the roentgenogram. The babies were all first-born children, and it is to be assumed that the deliveries were more difficult than is usual in the case of a multipara delivered by similar presentation. Recovery was spontaneous within four to twelve weeks, and no special treatment beyond heat and the prevention of contracture was required. The injury was due, in their opinion, to (1) too strong traction on the extremity; (2) a twisting pull on the limb; (3) inequality of distribution of traction in bringing down both feet, or (4) too hasty attempt at delivery. The pathologic condition, as interpreted from the roentgenogram, was a tearing or stripping of the periosteum of either the femur or the humerus at its weakest point of attachment, the epiphysial line, with maximal stress on the proximal epiphysis. With increasing trauma, a greater part of the periosteum of the shaft was stripped. The roentgenograms at first showed normal conditions but later indicated the extent of subperiosteal stripping, after calcium salts were deposited in the subperiosteal hemorrhage. Their second case is pertinent to this subject. A subperiosteal hemorrhage elevated the periosteum of the femur, and ossification occurred beneath this stripped periosteum. The area of periosteal stripping covered most of the femoral shaft. It was widest near the line of the distal femoral epiphysis and tapered gradually proximally. The distal epiphysis was not displaced. The line of the old shaft was visible when the child was 26 days of age, surrounded by the triangular area of subperiosteal ossification. A new

shaft had been reconstructed at the age of 4 months, the cortical lines of the old shaft gradually melting away. The new shaft was a part of the old shaft and a part of the newly formed subperiosteal bone. The unneeded bone had been resorbed.

A greater injury can dislocate the lower femoral epiphysis. This is a very rare injury, and only 3 cases have been reported.

Poland [3] in his work on traumatic epiphysial separations made note of such an injury. He noted the dislocation in a fetus. He cited Mme. La Chapelle's case in which excessive traction on the foot during delivery caused a separation of the lower femoral epiphysis and the upper tibial epiphysis. The child was born dead. A specimen in the museum of the Westminster Hospital shows the left femur of a full term fetus. The distal femoral epiphysis had been violently separated and the periosteum of the shaft stripped. The middle of the shaft of the femur was incompletely fractured transversely. No history of the specimen is available.

REPORT OF CASES

CASE 1 (Truesdell [4]).—The infant was delivered by version and breech extraction because of central placenta praevia. It was difficult to deliver the after-coming head, and the body was manipulated vigorously for a long time. The right thigh was swollen and tender two days later. A roentgenogram showed an outward and backward dislocation of the lower femoral epiphysis, as indicated by the position of its center of ossification. This roentgenogram was not taken for ten days, since it was believed that the baby had an infection of the thigh. No operation was done, because the mother could not nurse the baby. A dressing was applied. Just what type of dressing was put on was not indicated, nor was the position of reduction of the limb. A roentgenogram taken when the child was 2 weeks old showed that the knee was maintained in flexion.

New bone formation about the femoral shaft was evident at the age of 2 weeks. This subperiosteal ossification extended the length of the femoral shaft and was widest at the level of the distal femoral epiphysis. The child was observed for seven months, at the end of which time it died of bronchopneumonia.

Periodic roentgenograms showed reconstruction of the femoral shaft. At the age of 2 months the femoral shaft was spadelike, thickened by the new periosteal bone. This new bone extended for a distance of three quarters of the shaft. The femur was shaping itself so that it was meeting the displaced epiphysis. At the age of 6 months the femur was still different from the normal. It looked shorter and had an anterior curvature. A new medullary cavity was forming. The epiphysis was centrally placed beneath two well formed condyles. This had been accomplished by absorption of the unneeded part of the femoral shaft. The new shaft was a combination of new periosteal bone and original shaft.

Truesdell believed that nature, unassisted, can cope successfully with this disability.

3. Poland, J.: Traumatic Separation of the Epiphyses, London, Smith, Elder & Co., 1898, pp. 678, 683, 684 and 692.

4. Truesdell, E. D.: Birth Fractures and Epiphyseal Dislocations, New York, Paul B. Hoeber, 1917, p. 111; Report on a Case of Birth Dislocation of the Lower Femoral Epiphysis, Bull. Lying-In Hosp. 9:327, 1914.

CASE 2 (Massart [5]).—A boy was born at full term, by breech delivery. The accoucheur informed the parents that swelling of both thighs was present at birth. Labor was difficult and lasted thirty-six hours. Massart saw the baby when it was 36 days old. Both thighs near the knees were swollen in the form of cones with distal bases. Palpation of the swollen thighs was painful. Flexion of both knees was complete, but extension did not go beyond 90 degrees. A roentgenogram taken at the age of 18 days showed the distal epiphysis of each femur to be placed posteriorly in the lateral view but centrally in the antero-posterior view. The displacement was of no great degree but was more marked on the right side. The periosteum of each femoral shaft was stripped for three fourths of the length of the bone. Subperiosteal ossification was wider distally. In the belief that the lesion was syphilitic, the baby was given mercurial treatments despite the fact that the mother's Wassermann reaction was negative. At the age of 10 months there was no increase in the volume of the femur. Motions of the knee were full. There were so signs of syphilis.

CASE 3 (Pincherle [6]).—The mother, a primipara, was delivered of her baby in podalic presentation with the aid of a midwife. During the delivery the baby's legs were flexed at the knees and the thighs flexed at the hips. The midwife said she used no traction on the limbs. Pincherle saw the child when it was 14 days old. The child did not move the lower extremities spontaneously, and passive motion of the knees was limited and painful. Both knees were swollen, and the swelling extended to above the supracondylar region of the femur. The exact time of onset of the disability was not known to the parents. A roentgenogram taken at the age of 11 days showed posterior displacement of both lower femoral epiphyses. There was extensive subperiosteal stripping of the femoral periosteum, and a great deal of subperiosteal ossification was present. At the age of 3 months it was noted that the epiphysis of each side was in proper position and that the periosteal new bone was in regression. There was remodeling of the shaft. The lower third of the femur was angulated in such a manner that the epiphysis was brought under it. It was also broadened. Conservative therapy was used. Both lower extremities were first put in traction, and successive casts were then applied, each one bringing the knee into more extension. The casts were discontinued at the age of 2 months, and at this time motion of the knees was free and painless. A fusiform thickening of the lower end of the femur still remained.

CASE 4 (Our Own Case).—A primipara was delivered of a boy by breech presentation on Aug. 2, 1936, at the Flushing Hospital in Queens. The baby weighed 6 pounds and 7 ounces (2,948 Gm.). Within the first three days it was noted that the left lower extremity was limp and that the region of the left knee was swollen. A roentgenogram taken August 5 (fig. 1) showed a posterior and lateral displacement of the distal femoral epiphysis. Manipulation of the knee without anesthesia was tried by Dr. Langsam at the age of 3 days. This was not successful. Another manipulation was tried at the age of 7 days, with the baby under ether anesthesia at the Flushing Hospital, by Dr. Burman. This was done under fluoroscopic control. The joint space was widened medially by putting the knee into 45 degrees of valgus and into full flexion, downward and

5. Massart, R.: Décollement epiphysaire de l'extrémité inférieure des deux fémurs consecutif à un traumatisme obstétrical, Bull. Soc. anat. de Paris **18**:498, 1921.

6. Pincherle, B.: Distacco epifisario inferiori bilaterale del femore da trauma ostetrico, Pediatria **44**:816, 1936.

lateral pull being made on the epiphysis. This was done to provide a space for the reception of the epiphysis anteriorly. This part of the maneuver increased the deformity by mobilizing the epiphysis. The epiphysis was then pulled anteriorly and medially, and at the same time the knee was extended and put in about 5 degrees of varus to lock the epiphysis in its new position. The knee, however, could not be completely extended even with the baby under anesthesia. A hip spica was then applied. This procedure was only partly successful because of the fixity of the epiphysis. The inability to reduce the epiphysis completely was verified by roentgenograms taken immediately after the procedure.

The baby was admitted to the Hospital for Joint Diseases on August 13, when he was 11 days old. His general health was excellent. The left knee was swollen and showed a flexion deformity which prevented extension beyond 90 degrees. Flexion was full and painless from this limited position of extension. The knee was held in about 20 degrees of valgus but could be passively abducted to 45 degrees. The configuration of the knee was altered so that the upper, or femoral, part seemed more anterior, while the lower, or tibial, part seemed more

Fig. 1.—Left, roentgenogram of August 5, taken when the child was 3 days old. There is no subperiosteal calcification as yet. The distal femoral epiphysis is displaced posteriorly and somewhat laterally. Right, roentgenogram of August 10, eight days after birth. Subperiosteal ossification, which is greatest posteriorly and widest at the base of the epiphysial line, extends about halfway up the shaft of the femur.

posterior. Most of the swelling was on the medial side of the lower end of the femur. The skin at one point medially was dead white and surrounded by a zone of bluish discoloration the size of a dime, as if the underlying and anteriorly placed femur were about to perforate the skin by pressure necrosis. The left knee measured 6 inches (15 cm.) at the point of greatest swelling; the circumference of the right knee with the knee held in similar position was 4½ inches (11.3 cm.). With the knee in the flexion position there was a marked side to side movement, a little more than in the normal right knee. Manipulation of the knee seemed to be painful.

A roentgenogram taken August 10 (fig. 1) showed a marked posterior and a lesser lateral displacement of the lower femoral epiphysis, as indicated by the position of its oval center of ossification. There was an extensive subperiosteal hemorrhage which extended a little more than half way up the shaft of the femur.

The area of subperiosteal ossification was widest near the lower femoral epiphysis and greatest posteriorly and laterally; the lines of the shaft of the femur were clearly visible.

In view of the failure of manipulation, open reduction of the displaced epiphysis (by Dr. Burman) was resorted to on August 15 with the baby under general anesthesia. The Esmarch bandage and tourniquet were used to make the operative field bloodless. The joint was opened by the usual median parapatellar incision. This incision was used rather than any other because the lower femoral epiphysis is a part of the knee joint. The quadriceps muscle was diffusely edematous, pale and friable; it was hemorrhagic in occasional areas. The tendon of the quadriceps could not be clearly defined, and an incision was made through the muscle substance in the line of the cutaneous incision. A small amount of clear fluid escaped when the joint was opened. The lower end of the femur, which was red and beefy, was displaced anteriorly and medially. The entire lower femoral epiphysis was dislocated, and no part of the epiphysial plate was attached to the stump of the femoral shaft. The epiphysis was placed posteriorly and somewhat laterally, and a little upward (proximally) behind the shaft of the femur. The epiphysis was tilted obliquely in valgus of 20 degrees, with no particular rotation of the epiphysis, although its medial end seemed a little more anterior than its lateral end. Its condyles were perfectly formed and were an integral part of the knee joint. The meniscuses were not examined. The anterior and posterior crucial ligaments were normal. A little of the grayish tissue of the epiphysial plate was seen anteriorly and proximally, as if it had been squeezed out. The epiphysis was fixed firmly by scar tissue so that it could not be moved by the moistened, gauze-covered finger or by a skin-towel clip. The adherent tissue was carefully dissected away, especially posteriorly and laterally. To mobilize the epiphysis it was necessary to cut the internal lateral ligament at its point of origin. In dissecting away the adherent posterior portion of the capsule, close dissection was necessary to avoid the popliteal artery. A superficial flake of cartilage was cut away posteriorly. After this dissection had been done, it was easy to mobilize the epiphysis and to put it into its normal position, light lateral pressure being made on the lower end of the femur. A thin tongue of bone was present on the anterosuperior and lateral part of the epiphysis. A suture was placed through this tongue of bone and through muscle; when the suture was tied, the epiphysis was kept snugly in place. Another suture was taken medially through the point of origin of the internal lateral ligament and through muscle; after this suture was tied the ligament was taut, and the lateral instability of the knee was overcome. The wound was closed in layers, suturing being a little difficult because of the friability of the tissues. Configuration of the knee was restored after reduction. The knee was immobilized by a hip spica of plaster of paris, the knee being held in full extension and in 5 degrees of varus. The foot was placed in plantar flexion to relieve any strain on the back of the knee.

The postoperative course was uneventful, and the wound healed by primary intention. The baby was bottle fed by an appropriate formula. A postoperative roentgenogram showed that there was still some displacement of the epiphysis, indicating slipping of the epiphysis during the application of the cast. A roentgenogram (fig. 2) was taken when the cast was removed, just before manipulation. The lateral view showed the epiphysis still posteriorly placed but to a lesser degree than before operation; the anteroposterior view showed a lateral displacement of the epiphysis. Subperiosteal ossification was more evident and was especially marked posteriorly and laterally.

The knee was manipulated without anesthesia, under fluoroscopic control, on August 20. The epiphysis was movable, and only with the knee in extension could it be made to approximate its normal position. With the knee in flexion it slipped posteriorly. The epiphysis was easily displaceable. A hip spica was again applied after the epiphyses had been normally placed. Because of the easy mobility of the epiphysis, however, it could not be made certain that the
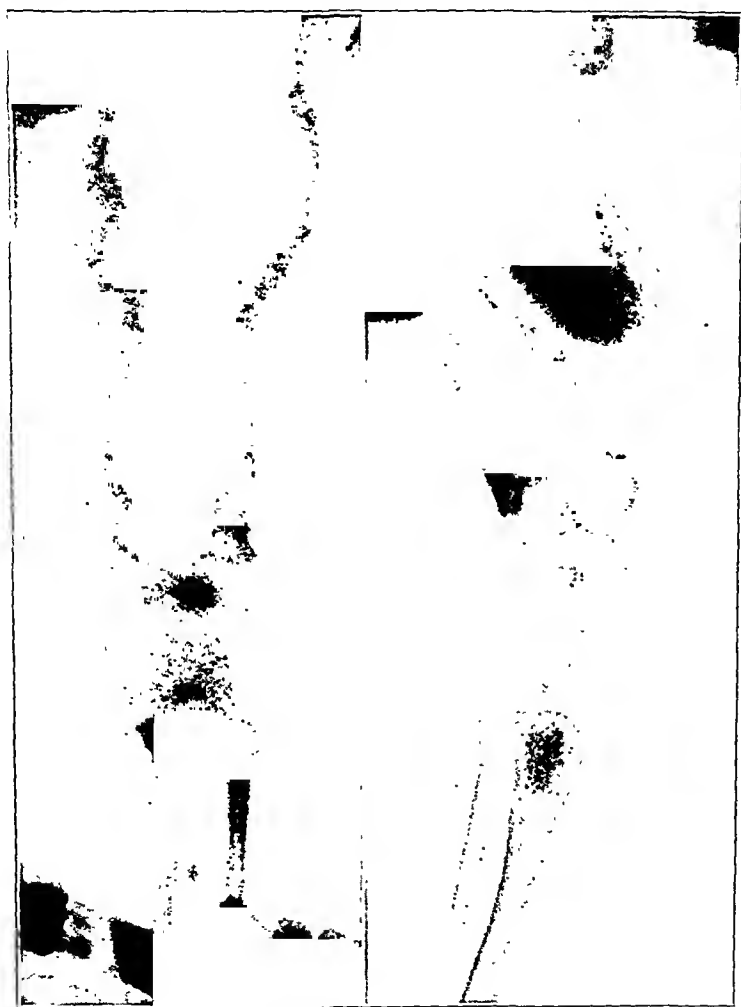
Fig. 2.—Roentgenograms of August 20, five days after open reduction of the displaced epiphysis. The epiphysis is still placed posterolaterally, but in the anteroposterior view there is beginning central placement of the epiphysis by an increase in the subperiosteal bone laterally.

exact placement of the epiphysis had been maintained. The roentgenogram of August 26 showed central placement of the epiphysis in the anteroposterior view but still some posterior displacement in the lateral view. The plaster was wedged at the knee joint to increase extension. On September 10 the hip spica

was removed. The alinement of the knee seemed good, but there was still some anterior prominence of the lower end of the femur. The femoral shaft was thickened in its lower third. A deep crease was present at the upper part of the tibia, and it was in this region that most of the effect of the wedging
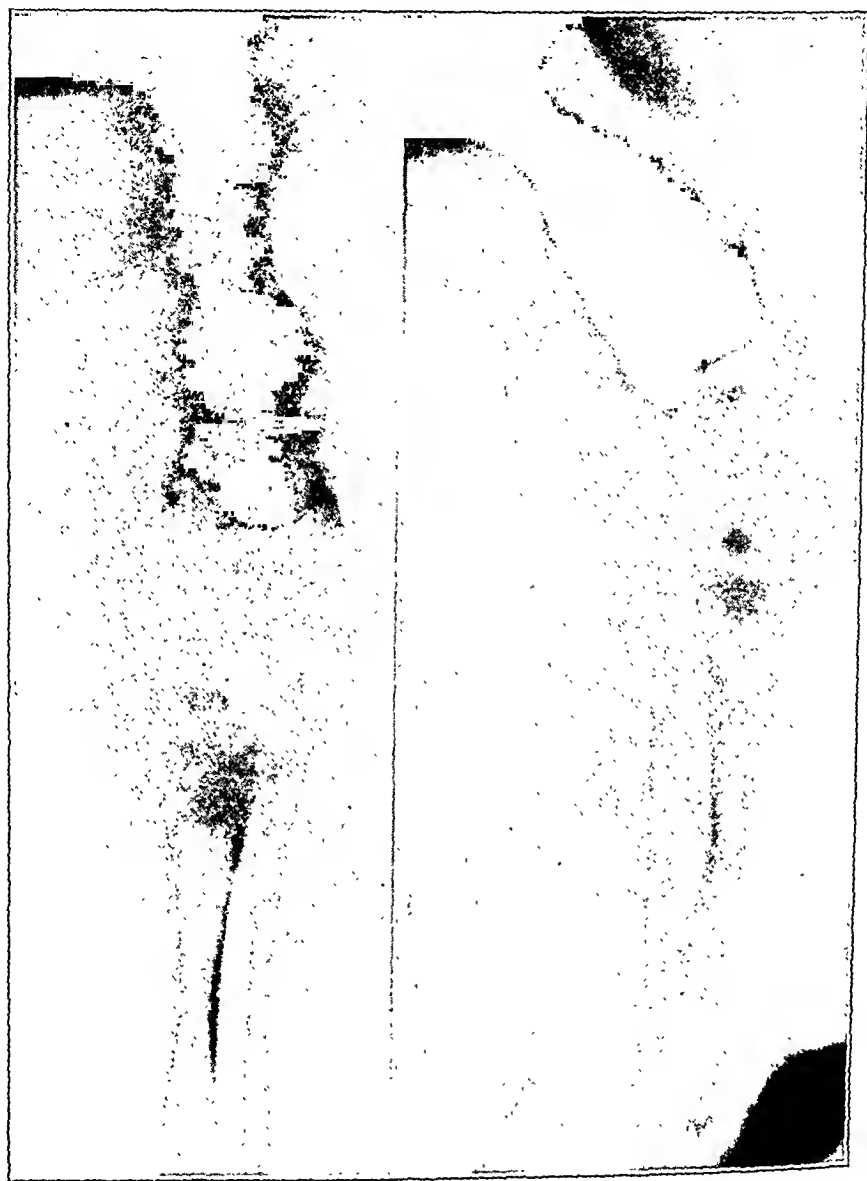
Fig. 3.—Roentgenogram of September 10. The epiphysis is now placed centrally. A greater amount of subperiosteal bone, which has formed posteriorly and laterally, has broadened the shaft so that it covers the epiphysis. The femoral shaft shows an anterior convexity which is due to posterior bending of the lower part of the shaft, its purpose being to meet and cover the displaced epiphysis. The lines of the femoral cortices are less distinct.

had taken place, although the site of wedging had been verified by roentgen examination to be at the knee joint proper. Extension was 165 and flexion 145 degrees. Wedging of the cast had been ineffective on the displaced epiphysis.

The roentgenogram of this date (fig. 3) was instructive. The lower half of the femoral shaft was much wider than usual because of the great amount of subperiosteal bone. The cortices of the femur were losing their distinctness and being gradually absorbed. The epiphysis was centrally placed in both the anteroposterior and lateral views. This had been accomplished by the new periosteal bone, which had grown so as to place the epiphysis centrally. There

Fig. 4.—Roentgenogram of November 7. The epiphysis is centrally placed in both the lateral and the anteroposterior view. The shaft has been remodeled, and the lines of the cortices of the femoral shaft are gone.

was more new bone formation posteriorly. In the lateral view the lower end of the femur was hollowed, but in the anteroposterior view it was straight. The lines of the femoral condyles were not distinct.

A long leg cast was applied with the knee held in extension. This cast was removed on October 3. The child was examined periodically. On November 7

extension was 175 and flexion 80 degrees. The right lower extremity (anteriorly) measured 9¼ inches (23.5 cm.); the left lower extremity (anteriorly), 9⅜ inches (23.8 cm.). The circumference of the right thigh was 6⅜ inches (16.2 cm.), and that of the left thigh, 6¾ inches (17.1 cm.). The legs seemed equal in length, and the external configuration of the knee was normal. The roentgenogram of that day (fig. 4) showed central placement of the epiphysis. Almost total remodeling of the femoral shaft had taken place. The cortices of the shaft could just be seen. The new shaft was wider than normal, showed an anterior convexity and was a compound of the old shaft and the new periosteal bone. The lower end of the femur was hollowed opposite the center of ossification of the epiphysis, and the lateral femoral condyle was more pronounced than the medial.

On Feb. 27, 1937, the child was about 7 months old. Extension was about 175 degrees, and flexion was complete. There was no lateral or medial deviation of the knee. The length of both lower extremities was 10¾ inches (27 cm.).

Fig. 5.—The two left films were taken May 22, 1937. This lateral view shows both the normal right knee and the left knee. The femoral shaft is completely remodeled and is somewhat atrophic. The epiphysis is centrally placed and equal in size to that of the right knee. On the right are anteroposterior views of the knees, of the same date. The left femoral shaft has been completely remodeled. It is atrophic and a little narrower distally. The epiphysis is centrally placed, but the epiphysial line is slightly irregular and is tilted upward and medially.

On May 22, 1937, at 9 months and 25 days of age, the baby still showed a mild thickening of the lower end of the femur. Both lower extremities were 11⅝ inches (29.5 cm) in length. The circumference of the right thigh was 8¼ inches (20.9 cm.) and that of the left thigh 8½ inches (21.5 cm.). Flexion was complete. There was no lateral instability of the knee. The contour of the knee was normal. The patella was normal in shape and normally movable. Both legs were slightly bowed. A roentgenogram of this date (fig. 5) showed some atrophy of the now completely remodeled shaft. The distal end of the bone was a little narrower than that of the normal right femur. The epiphysis was properly placed, but it was tilted slightly upward and internally by a medial obliquity of the slightly irregular epiphysial line.

The child was last examined fourteen months after operation. He walked well. The angle of greatest extension was still 175 degrees, flexion of the knee being complete. The knee showed no lateral instability. There was now shortening of ½ inch (1.2 cm.).

The roentgenogram showed no irregularity of the epiphysial line, but the epiphysis was still tilted obliquely so that its medial end was more proximal than its lateral end. The epiphysis was centrally placed. There were slight fuzziness and fragmentation medially and superiorly, suggesting an osteochondritic change. The lower end of the femur was bent posteromedially. The posterior surface of the distal part of the femur, just proximal to the epiphysial line, was somewhat irregular. A line of increased bony density was noted, running from the middle of the distal part of the femoral shaft obliquely, proximally and laterally to end about 1 inch (2.5 cm.) above on the lateral side of the distal part of the shaft.

COMMENT

Posterior dislocation of the lower femoral epiphysis is a birth injury conditioned by severe trauma during prolonged delivery by breech presentation in primiparas. This dislocation is the reverse of the usual anterior (cartwheel type) dislocation of this epiphysis in adolescents. The attachment of the two heads of the gastrocnemius muscle tends to pull the epiphysis posteriorly after it has been separated. The femur was not fractured in any of the living babies. The deformity, then, is a flexion deformity of the knee, with more or less valgus of the knee, conditioned by the epiphysial displacement in valgus.

The sex of the babies was mentioned in only 2 cases. Both infants were boys. The swelling of the knee joint and of the femur adjacent to it was noted at various times after delivery—immediately, within two days and presumably later. The involved lower extremity was limp, and the passive motions of the affected knee were painful. There was no reason to suspect an infection of the thigh since the soft tissues were not red or hot.

The epiphysial injury was unilateral in 2 cases and bilateral in the other 2. Such an injury is invariably accompanied by severe subperiosteal stripping, with early ossification of the hemorrhage. This develops quickly. It is seen already to be advanced in roentgenograms taken from eight to eighteen days after birth. The subperiosteal hemorrhage may be more severe than the epiphysial dislocation, as in Massart's case. It is this periosteal new bone which alters the shape of the femur and by its greater formation posteriorly and sometimes laterally tends to place the epiphysis centrally again. The lower part of the femur usually bends posteriorly to meet the displaced epiphysis. This produces an anterior convexity of the distal femoral shaft. This happens no matter what form of treatment is given. A period of two or three months elapses before the central placement of the distal epiphysis is completed.

Since nature itself remedies the defect, only the simplest treatment need be given, either traction or a cast holding the knee extended. In Massart's case, no treatment was given beyond mercurial rubs. In Truesdell's case the limb was bandaged in flexion, a position of the knee which increases the deformity; yet in both cases good results were obtained by the remodeling of the shaft of the femur. Within a few months the shaft is remodeled and the epiphysis centrally placed. Remodeling of the shaft of the femur begins after five to nine weeks. This is complete within a period of nine months, although in 1 case it was almost complete when the child was 9 weeks of age. Manipulation or open reduction is not indicated, and this is not refuted by our own experience. There is, however, a great temptation to try these measures.

The time for restoration of function is variously estimated between the ages of 2 and 10 months. In 1 case it was noted that motion of the knee was free and painless at the age of 2 months. In another, at 6½ months there was still slight restriction of extension. The baby in our case showed restriction of extension of 1 or 2 degrees when almost 14 months of age. The prognosis is excellent for useful function of the injured part.

The extent of damage sustained by the epiphysial plate is problematic. In no case is the answer in terms of shortening or deformity given. In our case, which has the longest follow-up, there is an upward and inward inclination of the epiphysial line. Resultant deformity may or may not develop, but theoretically it is probable.

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ENDOMETRIOSIS

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Endometriosis, or adenomyoma, does not occur frequently as a clinical entity. However, it can no longer be regarded as a pathologic curiosity. Cullen in 1,283 cases of myoma found adenomyoma in 73, or 5.7 per cent. MacCarty and Blackman at the Mayo Clinic reported a series of 3,398 cases of fibromyoma, in which 211, or 6.4 per cent were instances of endometriosis. Tyrone reported similar statistics. Sampson reported 332 laparotomies, with endometrial implants in 98 or 29 per cent. This percentage is high, but endometriosis is his specialty and he has constantly been looking for these lesions. His classic work has established endometriosis as an important condition. Statistics show that in the majority of cases the condition is undiagnosed before operation. With this point in mind, I reviewed the literature and analyzed the cases of endometriosis observed at the St. Francis Hospital and the Sedgwick County Hospital from 1931 to 1937 with the hope of reemphasizing the causes, diagnosis and treatment of endometriosis. I was able to collect 29 cases.

The term endometriosis has been defined by Novak as that condition in which endometrial tissue occurs aberrantly, that is, outside of the uterine cavity. This definition is broad, for it includes conditions in which the uterine musculature is invaded, as in Cullen's adenomyoma; Bell's adenomyosis; Bailey's endometrioma; mullerianoma; chocolate cysts, and tumors of the inguinal canal or of the umbilicus.

The various locations of endometriosis are well illustrated by Cullen's diagram (fig. 1). In this series of 29 cases there were 19 in which the condition was intrauterine and 10 in which it was extrauterine. The extrauterine lesions were located as follows: in the ovaries, 3; in old scars, 2; in the sigmoid flexure of the colon, 1; in the inguinal canal, 2; in the umbilicus, 1; in the tubes, 1.

Sites of the lesion in other series are given in the accompanying table.

ORIGIN

There is a difference of opinion as to the mode of origin of the various endometrial lesions. It is difficult to find one theory that satisfactorily explains such tumors. The first case of adenomyoma of the uterus was reported in 1860 by Rokitansky. Chiari described several cases in 1867 and said the condition was due to inflammation, such as

salpingitis or postabortal infection. Later (1896) von Recklinghausen reported cases of adenomyoma in which the condition was due to the embryonic rest from the wolffian system or mesonephron tissue. The presence of tumors in the pelvis and groin was thought to be the result of extension of the gubernaculum ovarii to the groin through the round ligament or canal of Nuch. This theory was superseded by
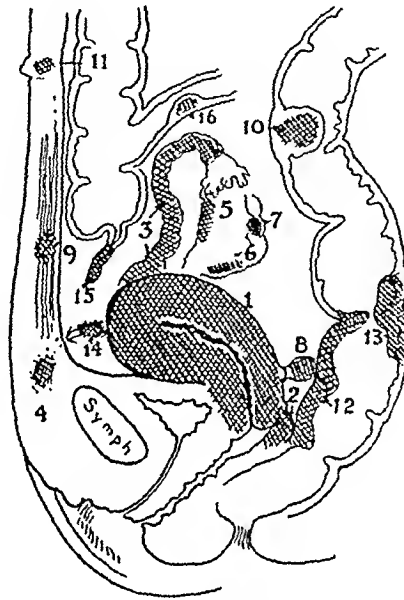
Fig. 1.—Sites at which endometrial lesions are found. This drawing illustrates the fact that no one theory has explained satisfactorily the origin of endometriosis. (After Cullen.)

Location of Endometrial Lesion

Location	King (70 Cases)	Keene (113 Cases)	Clark (29 Cases)
Uterus	17	0	19
Ovary	23	110	3
Tube	4	0	1
Peritoneum	26	0	0
Laparotomy scar	0	1	2
Umbilicus	0	2	1
Inguinal canal	0	0	2
Sigmoid	0	0	2

Cullen's invasion theory. In 1898 he definitely proved by serial microscopic slides that there is a communication between the gland spaces of the tumor and the uterine mucosa. In the same year, Ivanoff suggested the theory that endometriosis is a result of metaplasia of the peritoneal endothelium. The question is what causes the metaplasia. Witherspoon and Novak believe it is initiated by estrogen. In 1899 Russell reported the observation of endometrial tissue in the ovary and attributed its origin to aberrant portions of the mullerian ducts. Cullen agreed with this theory for extrauterine adenomyoma, and this is still

one of the most plausible theories. In 1903 Robert Meyers declared that endometriosis is the result of miliary abscess in the muscle wall of the uterus with ingrowth of the endometrial glands between the muscle fibers, supporting Cullen's invasion theory. The first case report in this series supports this theory. Meyer's theory is applicable to extrauterine growths, because the germinal epithelium of the ovary may undergo transformation into cylindric epithelium which microscopically resembles endothelium or uterine mucosa. Hertzler says this is expecting too much from the peritoneum.

In 1906 Sitzenberg published the theory that endometriosis is the result of proliferation of endothelial cells from the lymph channels. This theory was not recognized.
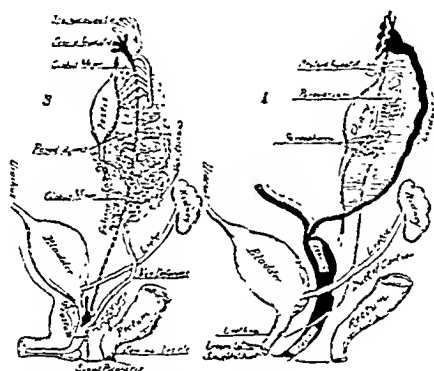
Fig. 2.—Diagrammatic sketch illustrating the many possibilities of the embryonic rest theory of endometriosis in the ovary and groin.

Sampson in 1921 published his implantation theory—that the menstrual endometrium is regurgitated through the tube into the peritoneal cavity, and in a suitable environment these endometrial cells develop into endometrial growths. The objection to this theory is that menstrual endometrium is not living tissue, and a chemical irritation would cause closure of the tube. It must be admitted that the endometrial growths occurring in scars after operation on the uterus or tubes (fig. 3) support this theory, but this endometrium is living tissue brought through by needle and suture. Jacobson's experimental work on transplantation of endometrial tissue in the rabbit also supports this theory. However, Hein was unable to produce the same lesion in the monkey, and the theory seems contrary to the principles of embryology and pathology.

Novak supported the theory advanced by Ivanoff and called attention to the origin of genital epithelium and peritoneum from the celomic

mesothelium.   He concluded that metaplasia is due to endocrine stimu-
lation, since it has been proved that estrogen influences the whole genital
tract, as is illustrated by treatment of vaginitis by estrone (theelin).

These theories have been listed to give an idea of the vast amount
of work that has been done on endometriosis.   No one theory entirely
satisfactorily explains the origin of the different lesions.

Fig. 3.—Endometriosis in a laparotomy scar after a suspension operation four
years previously.   Note the areas of miniature uteri.

PATHOLOGIC PICTURE

The gross picture of endometriosis varies.   There may be small areas
of glands causing no symptoms, or there may be extreme cases in which
the whole pelvis is filled with adenomyomatous invasion involving the
sigmoid flexure and the rectovaginal septum, simulating a malignant
tumor.   The uterus is usually two or three times the normal size
and is symmetrically enlarged, with tiny cystic areas scattered throughout
the muscle wall.   These cystic areas are dark brown, almost purple-

mulberry color, and contain blood, which at the time of menstruation finds its way to the uterine cavity; or if the growth is extrauterine it enlarges and causes more pain from distention of the miniature uteri.
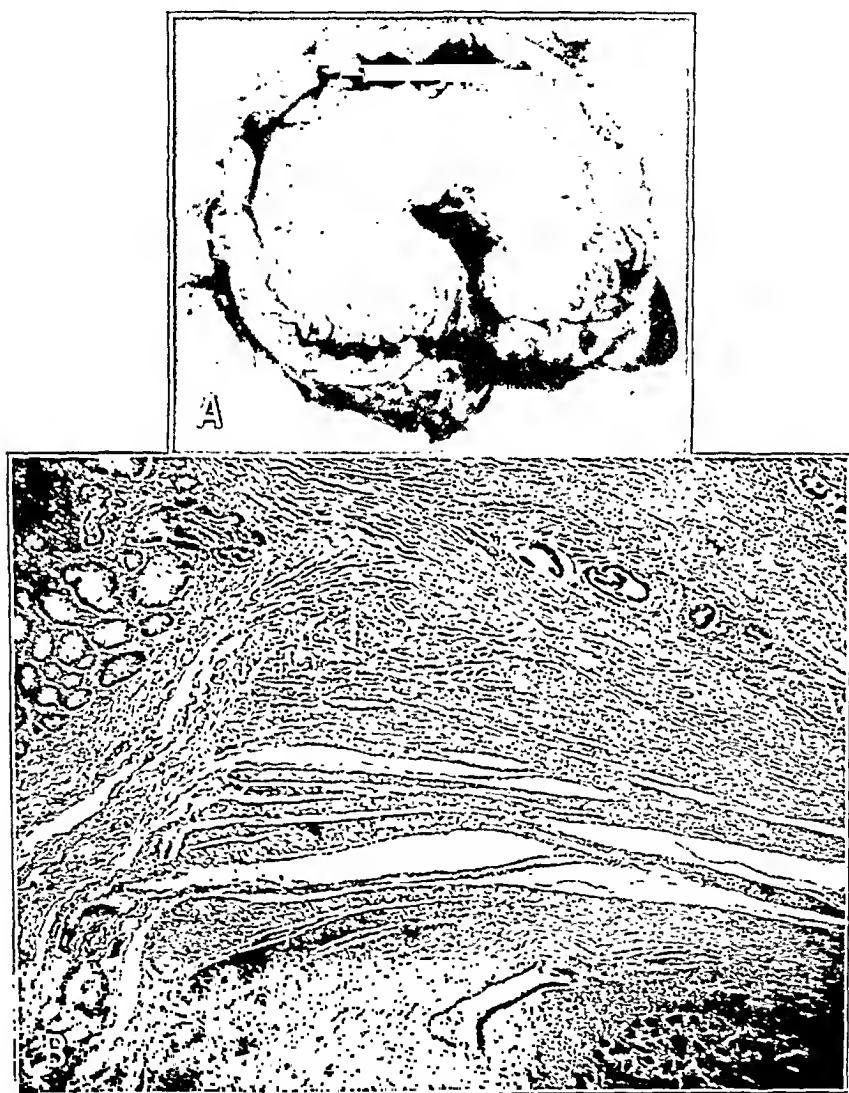
Fig. 4.—*A*, endometrial tumor in the wall of the sigmoid flexure of the colon, causing obstruction and death. *B*, high power microscopic section of the specimen *A*. Note the gland in the sigmoid and the areas of endometrial tissue.

Microscopically such a tumor consists of fibrous connective tissue and smooth muscle fibers. There are glandular spaces lined with cylindric epithelium like that in the uterine mucosa. These glands are

embedded in cellular stroma which is like that lining the cavity of the uterus, so that the tumor is similar to a miniature uterus. There is always evidence of hemorrhage or menstruation, and there are often wandering cells or clasmatocytes picking up the old blood cells (fig. 5).

SYMPTOMS

Endometriosis presents an interesting problem in differential diagnosis, well illustrated by the first case reported here. The patient in this case was treated for several different conditions by eight physicians over a period of four years, without relief. The condition is

Fig. 5.—High power microscopic section of endometrial tissue in the groin. Note the miniature uteri with the endometrium in the engorged state and the clasmatocytes picking up the old hemosiderin.

often puzzling and difficult to handle. One author reported a case in which curettage had been done twelve times in eighteen years. The condition was finally cured by a hysterectomy.

The symptoms and diagnosis depend entirely on the location and extent of the endometrial lesion. Undoubtedly, many lesions cause no symptoms and are not diagnosed until operation. In many cases a history of dilatation and curettage, abortion or infection may be a predisposing factor and may help in making a tentative diagnosis. Endometriosis often gives a picture similar to that of chronic inflammation of the pelvis and cannot be diagnosed until operation.

The lesion develops usually after the age of 25 and rarely after 60. In this study the youngest patient was 23 years old and the oldest 62.

Pain is the most constant symptom. It may be intermittent at first, but later it is more or less constant. In this series pain was present in every case, and in many instances the pain was referred to the rectum.

Dyspareunia, as with other pelvic conditions, is a common symptom.

Dysmenorrhea is a common complaint and usually comes on after the thirtieth year of life, becoming more severe with each period and sometimes associated with nausea and vomiting.

The menstrual history depends on the extent of the lesion. The periods become prolonged until there is more or less constant menorrhagia and metrorrhagia. Some patients with endometriosis are sterile, although 65 per cent of MacCarty and Blackman's patients had borne children and 38 per cent of the patients in this study had borne children. It is because of this menstrual disorder that Novak believes the cause to be an endocrine stimulation.

Many patients complain of vesical and rectal symptoms, and of course these symptoms should be investigated by special methods of examination.

The physical findings vary in relation to the pathologic condition present. Halban's sign is usually present—that is, enlargement of the uterus or ectopic tumor premenstrually and a return to normal after the flow subsides. This is due to the glandular stroma, which undergoes the same cyclic changes as normal endometrium. All of these symptoms are present in other pelvic conditions, but a careful correlation of the facts suggests endometriosis in many cases in which the lesion otherwise might not be diagnosed until a radical operation has been done for a suspected malignant tumor and the tissue has reached the pathologist.

TREATMENT

Since endometriosis occurs during the period of child bearing it is desirable to preserve ovarian function. It must be remembered that the tumor reacts to ovarian stimulation and in all cases is cured by castration. The treatment is conservative surgical management for the particular case. As has been pointed out, some such lesions cause no symptoms, but if they were allowed to develop, symptoms would probably appear. Small lesions are best treated with electric cautery and watched for recurrence. When the tumor involves the uterus a supravaginal hysterectomy gives the best results. When the growth involves other pelvic structures complete surgical removal gives the best results and would no doubt be considered a conservative procedure. The tumors regress after removal of the ovarian stimulation, but one must consider the acute

menopausal symptom and govern treatment accordingly. Many have reported pregnancies after conservative treatment of endometrial growths.

Roentgen therapy and radium therapy have been advocated by Bowing at the Mayo Clinic, but this would produce a cure only by completely destroying the ovaries, and I believe surgical intervention to be more conservative treatment, with a possibility of removing the growth and saving part of a functioning ovary.

Fig. 6.—Endometrial scraping after an abortion. The diagnosis was suppurative endometritis. Note the typical uterine glands infiltrated with leukocytes.

REPORT OF CASES

CASE 1.—A woman aged 20 was referred to me on Nov, 20, 1934. She had had an induced abortion one year before and had had more or less flowing most of the time since. She could not differentiate a normal period. There had been severe pelvic pain and backache. For the last two weeks the patient had been in bed because of increased flowing and clots. The past history was irrelevant. The menstrual history began at the age of 11. The menses were painful and lasted three or four days. Her physician had tried many bottles of ergot and also dilation and curettage and many hypodermic injections of endocrine products, without results.

Physical examination gave essentially negative results. The temperature was 98.6 F.; the pulse rate was 96; the blood pressure was 100 systolic and 44 diastolic. The hemoglobin content of the blood was 66 per cent, and the erythrocyte count was 3,100,000. The vagina was normal. The cervix showed good position and was ircely movable. The uterus was normal in size and position.

The diagnosis was incomplete abortion. I advised curettage, which was done November 20. The patient made an uneventful recovery. She was discharged November 25.

Pathologic Report on Endometrium.—The mucous membrane of the uterus was partly necrotic and heavily infiltrated with leukocytes, lymphocytes and plasma

Fig. 7.—High power photomicrograph of the specimen in figure 6, showing areas of necrosis and inflammatory cells.

cells. The blood vessels were enormously dilated. The glands were wide and tortuous like those one sees in pregnant women. There was no definite placenta tissue. The diagnosis was acute suppurative endometritis; so I felt the symptoms were caused by chronic pelvic inflammation (figs. 6 and 7).

The bleeding continued in spite of ergot preparations and endocrine therapy. Consultation was held, and it was decided to use roentgen therapy to stop this functional bleeding. The patient received an enormous amount. She moved to a neighboring town. She was again given roentgen therapy and many injections of endocrine substance to stop the continued bleeding. At times it would cease for weeks; then the period flow would be excessive and would last two or three
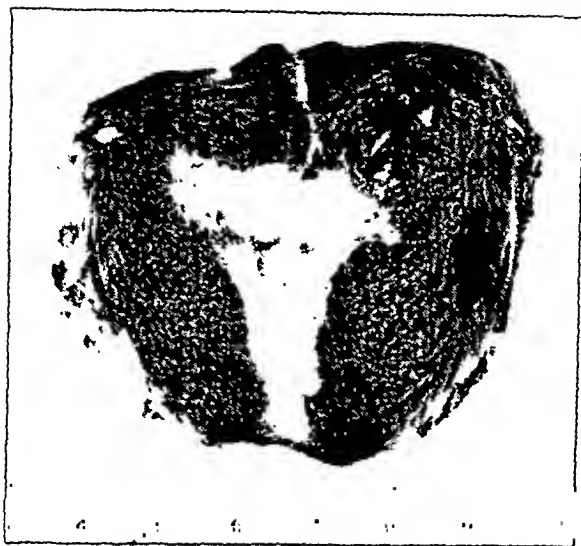
Fig. 8.—Small uterus removed after roentgen therapy. Note the dark areas of endometrial tissue in the muscle wall.
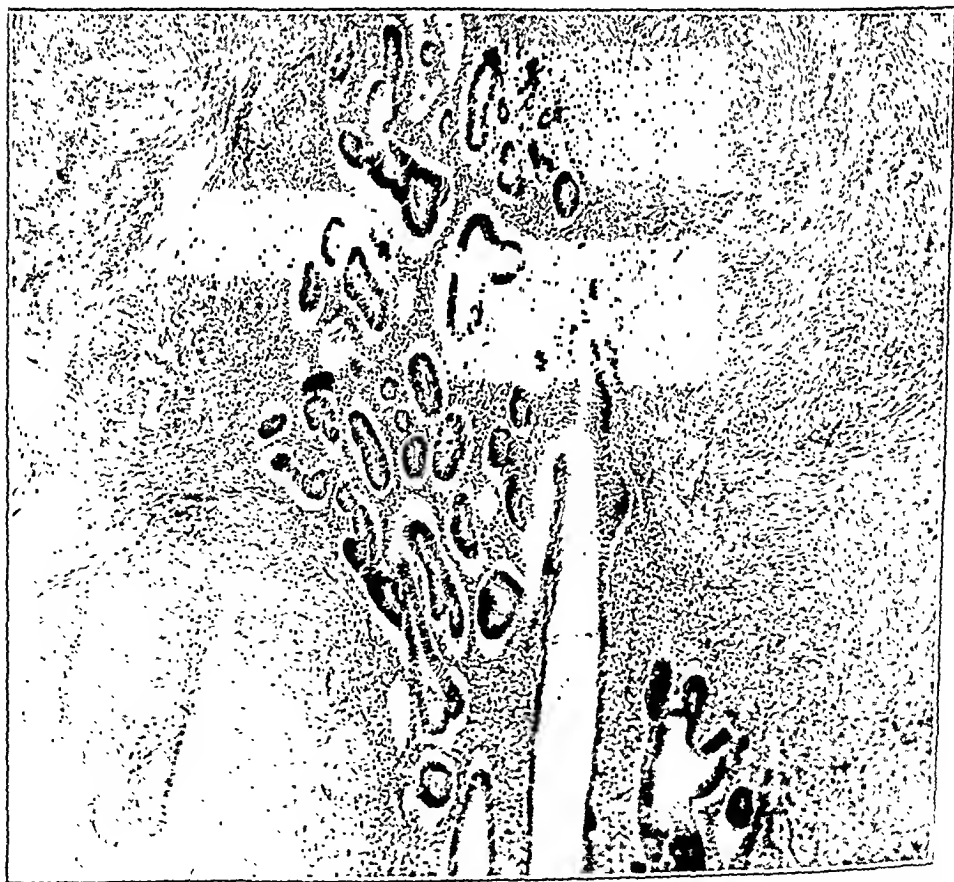
Fig. 9.—High power magnification of the specimen shown in figure 8. Note the islands of endometrial tissue, or miniature uteri.

weeks. She returned to me on Oct. 16, 1937, complaining of pain and continued flowing. Physical examination revealed a small uterus, freely movable. I considered a polyp and even a low grade malignant tumor of the body of the uterus. A diagnosis of endometriosis was considered, but the fact that the ovaries had been destroyed by the roentgen rays made me decide on a hysterectomy.

Supravaginal hysterectomy October 18 revealed a small uterus. The ovaries were the size of navy beans. The patient left the hospital free from symptoms of four years' standing.

Fig. 10.—Microscopic section of a cyst wall, showing areas of endometrial tissue. Such cysts usually rupture, pouring their contents, which are intensely irritating, into the peritoneal cavity, thus involving other organs.

The pathologic diagnosis was adenomyoma or endometriosis of the uterus. This case supports Meyer's inflammatory theory because of the pathologic condition found in 1934 (figs. 8 and 9).

CASE 2.—A white woman aged 25 entered the hospital complaining of severe pain, profuse menses and urgency and frequency of urination since an operation for the same symptoms in 1933. The uterus was partially fixed in the pelvis. The left ovary was the size of a tennis ball and was fixed to the bladder. At operation the condition of this ovary was seen to be typical of endometriosis, and the uterus showed areas of infiltration with small purple cysts.

After removal of the pathologic tissue the lumbar plexus was resected, and the patient left the hospital free from pain and symptoms.

The condition in this case can be explained by Novak's theory, as due to endocrine upset.

CASE 3.—A woman aged 46 complained of a small tumor at the umbilicus that became sore each month. A bloody discharge came from the umbilicus.

The diagnosis was clinical endometrioma.

A physician told her the condition would subside after the menopause; I am unable to verify this diagnosis with a microscopic section, but such tumors have been removed and typical endometrial tissue has been found to be the cause of the symptoms.

This case supports the metaplasia theory, and certainly the theory of origin in the wolffian system or in the mullerian ducts or the Sampson theory would not explain endometrial tumors of the umbilicus.

SUMMARY

The pathologic picture of tissue with histologic and functional characteristics similar to those of endometrium has been known since 1860, and yet many physicians are unfamiliar with the clinical entity. Various theories as to the origin of such lesions have been discussed, but no theory is satisfactory.

The symptoms depend on the extent of the lesion. However, pain, dysmenorrhea and irregular menstrual history, correlated with certain physical findings, strongly suggest an endometrial lesion. Early diagnosis will frequently obviate the necessity for extensive radical operation. The treatment of endometriosis is conservative operation.

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LEIOMYOSARCOMA OF THE URINARY BLADDER

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Sarcoma of the urinary bladder is an uncommon neoplasm, and leiomyosarcoma is even more uncommon. In a careful review of the literature we were able to find records of only 13 cases of leiomyosarcoma. The case to be reported here brings the total up to 14. It is possible that this list is not complete and that some cases may have been overlooked. Three cases, 1 reported by Albarran (1881) and 2 by Targett (1896), were referred to by Rabson; but, as he suggested, the evidence is insufficient for a positive diagnosis and hence they are not included in the present tabulation. Before discussing this subject in detail, we should like to report the following case.

REPORT OF A CASE

N. M., a man aged 55, single, was first admitted to the Presbyterian Hospital on Jan. 5, 1936.

The patient had had three attacks of gonorrhea, one of which was complicated by an attack of epididymitis on the left. A tonsillectomy was performed when the patient was 45 years of age and a herniorrhaphy on the right when he was 49.

The present illness began five years before the patient's first admission to the hospital. At the time of admission he complained of pain and burning on urination, frequency and urgency of urination, nocturia, difficulty in starting the stream, hematuria, backache and loss of weight. The symptoms were always aggravated by his becoming chilled or "catching cold," and they were definitely progressive.

The pain was present before and during urination and was referred to the glans penis. Burning occurred along the entire course of the urethra. Frequency of urination was so marked that the patient was finally obliged to urinate once every hour during both day and night. During the four years previous to admission he had had four attacks of complete retention of urine, so that catheterization was necessary. The last time he had been catheterized was four months before his admission to the hospital, since which time all his symptoms had become much worse. One month previously he had had three attacks of hematuria. During the previous four months he had lost 35 pounds (15.9 Kg.) in weight. Replaceable rectal protrusions had been prominent for a year.

Physical examination showed an anemic, emaciated patient. The head and neck were normal; the teeth were carious and in need of repair. The heart, the lungs, the abdomen and the external genitalia were normal.

Rectal examination revealed large hemorrhoids which protruded on straining. The tone of the sphincter was normal. The prostate showed enlargement of grade 4

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and was soft, smooth, elastic and slightly tender. No signs of carcinoma of the prostate were demonstrable.

The electrocardiogram showed ventricular extrasystoles and left axis deviation. A blood count showed: erythrocytes, 4,250,000 per cubic millimeter; leukocytes, 6,000, and hemoglobin, 85 per cent. The blood pressure was 135 systolic and 85 diastolic. Chemical studies of the blood showed the nonprotein nitrogen content to be 35.7 mg.; and the creatinine content 1.0 mg. per hundred cubic centimeters.

Examination of the urine showed the presence of albumin, the absence of sugar and a count of 2,050 red blood cells per cubic millimeter. Cultures showed short chain streptococci. No tubercle bacilli were found.

In the phenolsulfonphthalein test the time of appearance was six minutes. The total excretion in ninety minutes was 75 per cent.

Roentgen examination showed absence of stone in the urinary tract.

Intravenous pyelograms revealed bilateral hydronephrosis. The cystogram showed apparently normal conditions.

Cystoscopic examination (January 6) (with the region under local anesthesia) was very painful. The capacity of the bladder was limited. A large tumor was present, which seemed to be more or less papillary; because of the size of the growth the base could not be accurately defined, nor was it possible to determine whether or not there was a pedicle. The ureteral orifices could not be seen since they were covered by the tumor. A cystoscopic diagnosis of papillary tumor of the bladder was made, and a piece was removed for histologic study. This resulted in a diagnosis of papillary carcinoma.

Four days later (January 10), with the patient under sacral anesthesia, bipolar fulguration of the tumor was done with the Stern-McCarthy resectoscope.

Examination with the resectoscope on February 22 showed a large tumor. Many necrotic areas were seen, which were the result of fulguration. Resection of large masses of the tumor and also fulguration were carried out at this time.

On February 29 a transurethral resection of the prostate was done with the patient under sacral anesthesia.

The histologic diagnosis of some of the removed pieces was benign adenoma of the prostate.

The resection was followed by acute prostatitis and periprostatitis. In addition, a tentative diagnosis of acute pyelonephritis was made, and the patient was discharged from the hospital on March 20.

On April 4 the patient was admitted to the hospital for the third time, because of increased frequency of urination and pain in the lower part of the sacrum. A diagnosis of acute exacerbation of the prostatitis was made. The patient was discharged.

Four days after the previous discharge (April 17) the patient entered the hospital for the fourth time. Profuse hematuria was present; the urine was very bloody, and many blood clots were passed. In addition to the hematuria he had severe urgency and frequency of urination, severe pain in the lower part of the abdomen and pain on urination. It was necessary to administer codeine every three hours. Since all attempts to control the bleeding were of no avail, it was decided to perform a suprapubic cystostomy.

On May 5 a suprapubic cystostomy was performed with the patient under ethylene anesthesia. The perivesical veins were unusually large, tortuous and dilated, and the vesical wall was enormously thickened. Examination of the interior of the bladder showed a large tumor that almost completely filled the entire

vesical cavity. A piece of the tumor was removed for biopsy. A total of 5,511 milligram hours of radium was given. The patient was discharged on June 25.

The histologic diagnosis of the tissue removed at operation was carcinoma of the bladder.

The patient was admitted to the hospital for the fifth time on August 2. He had been fairly comfortable until twenty-four hours before his fifth admission, when he was seized with a severe attack of pain in the chest, some shortness of breath and a mild cough. Great emaciation and severe anemia were present. Diagnosis was made of an infarct in the lung. The patient left the hospital in ten days.
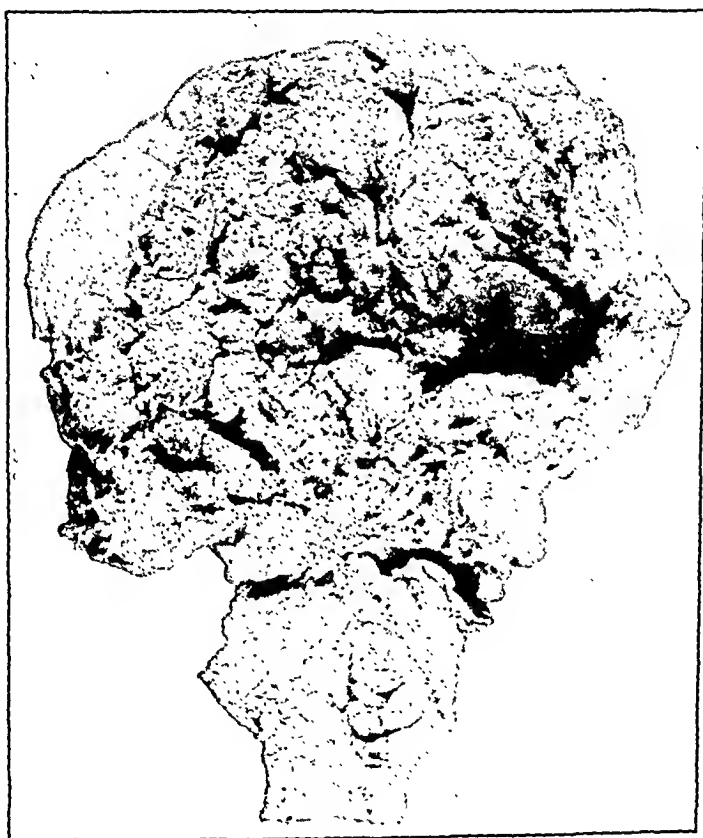
Fig. 1.—Autopsy specimen. The tumor almost filled the vesical cavity.

Subsequently, severe pain developed in the lower part of the abdomen, especially in the region of the bladder and rectum. The pain was excruciating and practically continuous. No relief was obtained from 1 grain of morphine or a combination of 1 grain of pantopon (a mixture of the hydrochlorides of the opium alkaloids) with 1 grain of codeine. The urine was very bloody. Apparently there was bleeding from the tumor. On account of the severe, uncontrollable pain, Dr. A. Verbrugghen was called into consultation, and it was decided to perform a chordotomy in the hope of instituting relief.

On Oct. 8 a chordotomy was done by Dr. Verbrugghen. After the operation, the patient had a very stormy convalescence: high fever, pain in the kidneys, severe diffuse abdominal pain and marked abdominal distention occurred. A diagnosis of acute pyelitis and pyelonephritis was made. The patient died on October 15.

Autopsy was performed by Dr. Carl Apfelbach. The anatomic diagnosis was as follows: leiomyosarcoma of the urinary bladder, with extensive dilatation of the lumen and ulceration and gangrene of the wall; spontaneous perforation of the urinary bladder; severe bilateral hydronephrosis and hydroureter; suppura-
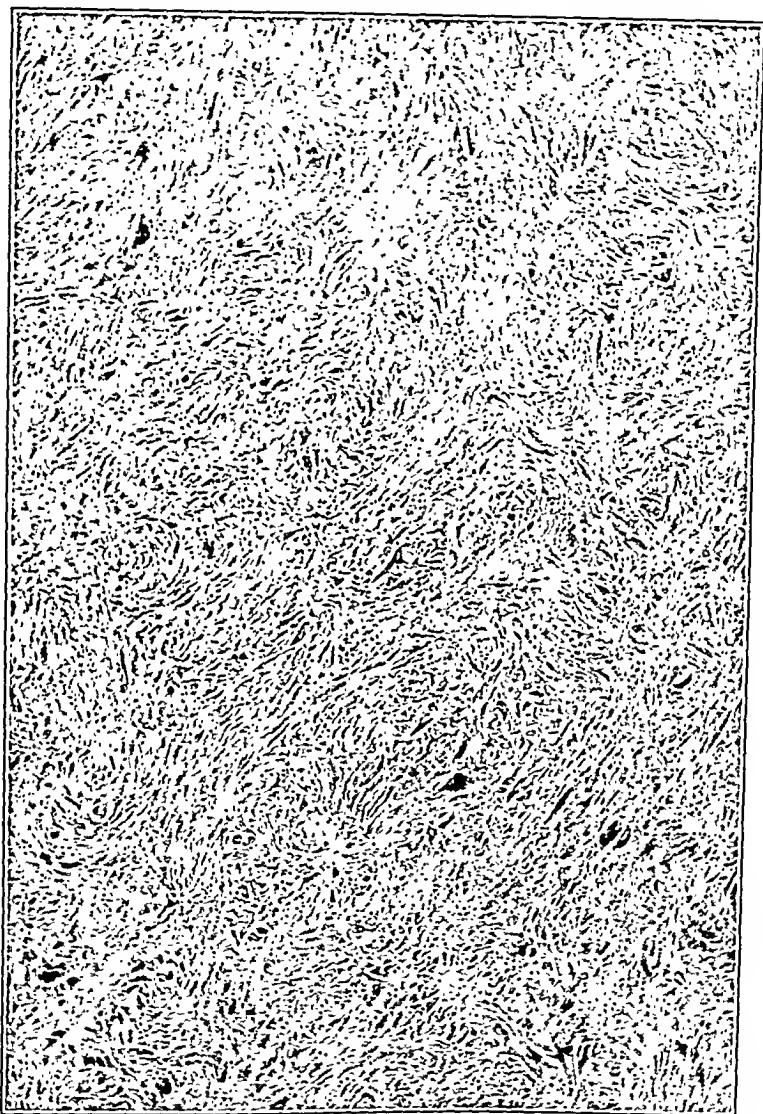
Fig. 2.—Low power photomicrograph of a leiomyosarcoma, showing spindle-shaped cells.

tive cystoureteropyelonephritis; two left renal arteries; acute generalized fibrino-purulent peritonitis; localized fibrous peritonitis; slight hyperplasia of the spleen; emaciation; anemia; chronic interstitial hepatitis; bilateral disseminated fibrous pleuritis; unhealed cystostomy wound; recent chordotomy; linear scars of the penile portion of the urethra; coal pigmentation of the lungs.

The capacity of the bladder was very large. The bladder was about twice
the normal size. The vesical wall was greatly thickened; in some areas it was
3 cm. thick. The tumor was irregularly shaped and soft; a large part was
discolored, the color varying from greenish brown to black; here and there

Fig. 3.—High power photomicrograph of a leiomyosarcoma, showing striations
of the neoplastic cells.

it was white. Some of the tumor masses were pedunculated. The lining of the
trigon and the prostatic portion of the urethra was grayish brown and firmer
than normal (fig. 1).

TABLE 1.—*Basis for Diagnosis in Previously Reported Cases of Leiomyosarcoma*

Case	Year	Author	Microscopic Description	Comment
1	1875	Gussenbauer (Billroth)	"Spindle cells which could not be differentiated from organic muscle cells: myosarcoma: rich in smooth muscle fibers. Interstitial cells of sarcoma and carcinoma. Smooth muscle cells showed activity of multiplication and grew by cell division. Young cells round and odd but transition forms between these and typical smooth muscle cells."	
2	1885	Eve	"Mixed or myosarcoma: 3 classes of cells: (1) large cells with spheroid nuclei, epithelioid but of connective tissue origin; (2) young cells of above; (3) nucleus elongated, mitosis, in process of formation of unstripped muscle fibers. Hyperplasia of all elements except epithelial. New formation of muscle fibers not most marked feature."	Rabson stated the evidence insufficient to diagnose leiomyosarcoma
3	1888	Nicolich	"Predominating tissue is smooth muscle. A large part of these cells are round; others oval or irregular: of varying size: the nuclei of many are fusiform to round, enlarged. Diagnosis—myosarcoma."	
4	1895	Klein	"Large, wide, very long spindle cells, small central nucleus: stand out definitely: longitudinal striation but no cross striation: large smooth muscle fiber. Tumor same as polypous sarcoma occurring in the vagina."	
5	1904	Lexer	"True myosarcoma, as has been frequently operated."	Rabson stated the evidence insufficient to diagnose leiomyosarcoma: Henke and Lubarsch include this case in their list
6	1904	Röder	"Smooth muscle fibers, easily recognized through rod type nuclei and protoplasm which stains intense yellow with Van Gieson. Also cells without particular character so that tumor could be called a true myosarcoma."	
7	1927	Burlakov	"Structure corresponds to that of smooth muscle tissue. Polymorphous cells, sarcomatous: consists solely of smooth muscle fibers. Falls between leiomyoma and true sarcomas: a polymorphous sarcoma-like leiomyoma."	

TABLE 2.—*Tumors of the Urinary Bladder*

Author	Tumors of the Bladder	Sarcoma	
		Number	Percentage
Albarran	89	2	2.25
Caulk	303	1	0.33
Davis	41	2	4.88
Egger	83	1	1.20
V. Frisch	300	1	0.33
Fuchs	136	1	0.74
Gardner	369	6	1.63
Geraghty	180	2	1.11
MacKenzie	228	1	0.44
O'Niel	62	1	1.61
Pack and LeFevre	522	2	0.38
Rabson (cases by Stepita)	860	2	0.24
Scholl	262	1	0.38
Total	3,435	23	0.67

Histologic Stricture.—Sections of the neoplasm were fixed in Zenker's fluid and stained with hematoxylin-azure-eosin, Van Gieson's stain, phosphotungstic acid–hematoxylin and Foot's modification of Bielschowsky's stain. The characteristic cell in the neoplasm was a large spindle-shaped cell several times as large as the normal fibroblast. The cells were arranged in interlacing bundles, but the structure only slightly resembled the usual parallel arrangement of muscle cells (fig. 2). In a large part of the neoplasm necrosis and gangrene had occurred. Consequently, there were only a few regions in which the finer details of the cells were still present. The nuclei varied greatly in shape, size and chromatin content. Some of them had nucleoli. There were a few multinucleated cells. Mitotic figures were sparse, and in some of the neoplastic cells the fibrillar arrangement of the cytoplasm was demonstrated.

In Van Gieson preparations the cytoplasm stained light yellow. Argentophilic fibrils were present in small numbers. Collagenous fibers were more abundant. The striations of the neoplastic cells were best demonstrated in preparations stained with phosphotungstic acid–hematoxylin (fig. 3).

COMMENT

It is not our object to discuss the subject of sarcoma of the bladder in general, since this has been the subject of several recent papers, to which those who are interested may refer. We shall limit our remarks to leiomyosarcoma, except as it may be necessary to refer to the general topic of sarcoma of the bladder.

We are mindful of the fact that in some cases reported as instances of leiomyosarcoma the diagnosis has been questioned by subsequent authors. We are also familiar with the fact that some of the questionable cases have been accepted without reservation by other authors; for example, the case of Lexer. Rabson stated that the evidence was insufficient to establish the diagnosis of leiomyosarcoma, whereas Henke and Lubarsch included this case in their list. Because of differences of opinion in regard to the early cases reported, it is thought desirable to present them in detail, in table 1.

The first case of sarcoma of the bladder was reported by Senftleben in 1861 and the diagnosis was confirmed by Billroth in 1905. Rabson in 1934 collected 234 cases of sarcoma of the bladder, and since then 48 additional cases have been reported. In a series of 3,435 cases of vesical neoplasm, collected from the works of thirteen authors, Rabson found only 23 cases of sarcoma (0.67 per cent). Pack and LeFevre in their study of 19,129 admissions to the Memorial Hospital found 522 vesical tumors, of which only 3 were not epithelial in origin, namely, 2 sarcomas and 1 leiomyoma, or approximately 1 sarcoma in 10,000 admissions.

The first case of leiomyosarcoma was reported by Gussenbauer from Billroth's clinic in 1875. Since then, 13 or more have been described. From the list of vesical sarcomas containing smooth muscle, 8 definitely were diagnosed by the authors as leiomyosarcoma; the other 6 (all

observed prior to 1904) were called myosarcomas, and in the micro-
scopic description of them all the authors described hyperplasia of smooth
muscle cells, although in one or two instances it has been stated that this
element by no means predominated. However, we felt that the tissue
they described would today be classified as leiomyosarcoma. In table 3
is presented a brief summary of the 14 cases of smooth muscle sarcoma.

The origin of vesical sarcoma is a matter of considerable disagree-
ment. Prentis and Arey suggested three methods of increase of smooth
muscle cells in the embryo: (1) formation of new cells from the mesen-
chyme; (2) transformation of the interstitial cells into muscle fibers,
and (3) multiplication of their nuclei by mitoses in the more advanced
fetal stage. Thus, smooth muscle tumors may arise in the adult by the
unrestrained growth of misplaced persistent mesenchymal cells (Cohen).

The theory has been advanced that myoma is of embryologic origin,
developing, according to various authers, from a partially atrophied
müllerian body (Verhoogen), from the urachus (Pilliet and Dupuy),
from supernumerary ureters (Riegal) or from a hydatid of Morgagni
or the lower layer of the utricle (Hegal). Because of the simplicity of
these theories of embryonal origin, Heitz-Boyer and Doré and later
DeBerne-Lagarde thought that they should be accepted. Blum sug-
gested that myoma develops from hypertrophied vesical musculature,
secondary to chronic inflammatory changes. Claisse (cited by Heitz-
Boyer and Doré) concluded that uterine fibroid is produced by peri-
vascular inflammation caused by infective agents acting on the walls of
the uterine vessels and that the same theory is applicable to vesical
tumors. The origin of leiomyoma of the bladder is undoubtedly related
to that of leiomyosarcoma.

In writing of leiomyosarcoma Cohen stated that the cells of this
tumor are shorter and rounder than those of a benign tumor. The
nuclei are massive and hyperchromic. Giant cell forms may exist. The
stroma is scanty, and the walls of the blood vessels are defective.
According to Evans, the occurrence of many mitotic figures is a reliable
sign of malignancy. Proper and Simpson classified malignant leiomyoma
into 3 groups and noted that the malignancy increases proportionately
through the following groups: (1) those closely resembling leiomyoma;
(2) those having short spindle-shaped cells with oval nuclei: and (3)
those having great variation in the morphologic character of the cells.

Cecil stated that vesical sarcoma frequently arises from the trigon or
the vesical orifice or from near these structures. Rabson concluded that
leiomyosarcoma (as contrasted with rhabdomyosarcoma) is more likely
to have a primitive origin in the wall of the urinary bladder. A glance at
table 3 will bear this out; of the 14 leiomyosarcomas, 13 were definitely
stated to have arisen from the vesical wall (in Burlakov's case the origin

TABLE 3.—*Data on Previously Reported Cases of Leiomyosarcoma of the Bladder*

No.	Year	Author	Sex of Patient	Age of Patient	Location of Lesion	Duration of Symptoms	Symptoms	Operation	Result	Autopsy	Metastases?	Author's Diagnosis
1	1875	Gussenbauer	M	12	Posterior wall	10 mo.	Pain; dysuria; frequency	Suprapubic resection	Left hospital 33 days after operation; well	Not stated	Not stated	Myosarcoma
2	1885	Eve	..	..	Right lateral wall	......	Specimen only	....				Myosarcoma
3	1888	Nicolich	M	47	On all walls	2 weeks	Pain; hematuria; frequency; dysuria	No operation	Bilateral hydronephrosis and hydroureters	Yes	Not stated	Myosarcoma
4	1895	Klein	M	10	Posterior wall	10 mo.	Pain; hematuria; dysuria		Death 3½ weeks after onset of symptoms; bilateral hydronephrosis and hydroureters	Yes	No	Myosarcoma
5	1904	Lexer	M	50	Right posterior wall	Not stated	Pain; frequency; urgency; abdominal tumor	Partial resection of bladder	Healed	Not stated	Not stated	True myosarcoma
6	1904	Röder	M	49	Lateral wall	4 yr.	Left inguinal pain on urination; palpable tumor in left pelvis (per rectum)	Partial resection of bladder and pedicle	Healed	Not stated	Not stated	True myosarcoma
.								Partial resection of bladder wall and urethra	Death 5 days after operation due to peritonitis	Yes	Not stated	True myosarcoma
7	1927	Burlakov	F	54	Bladder	Not stated		No operation	Death	Yes	Not stated	Sarcomatous myoma
8	1928	Hager and Hunt	F	53	Posterior wall	10 days	Hematuria (no frequency or pain)	Transperitoneal resection of bladder	Left hospital 24 days after operation; alive and well 4 yr., 2 mo. after operation	Not stated	Not stated	Leiomyosarcoma

9	1929	Caylor and Walters	M	4	Right superior and anterior lateral walls	8 mo.	Pain; hematuria; frequency and nocturia; dysuria; incontinence	Resection of wall	Recurrence 2 mo. after operation; death 3 mo. after operation	Not stated	Not stated	Leiomyosarcoma
10	1931	Mintz	M	5	Posterior inferior wall	4 mo.	Pain in stomach; hematuria; frequency; dysuria; vomiting	Suprapubic removal of tumor; palliative ureterotomy	Recurrence; death 1 yr. after operation (18 mo. after onset of symptoms)	No	Recurrence at site	Leiomyosarcoma
11	1932	Krauskopf	F	60	Filled bladder and true pelvis anterior wall	2 yr.	Pain; frequency; incontinence; slight loss of weight; increased size of abdomen	Exploratory laparotomy and removal of tumor	Death 35 days after operation due to auaria	No	Not stated	Leiomyosarcoma
12	1932	Powell	M	71	Right lateral wall	5 weeks	Hematuria; loss of weight (no pain, frequency or dysuria)	Resection of lateral wall	Discharged 6 weeks after operation; death 5 mo. after operation	Yes	No; recurrence at site and whole right trigon	Leiomyosarcoma
13	1937	Weyerbucher and Balch	M	4	Left lateral portion	1 week	Pain; hematuria; frequency; retention; straining	Suprapubic cystotomy for drainage; biopsy	Death 3 months after operation	Yes	To lungs	Leiomyosarcoma
14	1937	Kretschmer and Doehring	M	55	Bladder wall	5 yr.	Pain; hematuria; frequency; complete retention; loss of weight; backache; burning	Resection of tumor; fulguration; suprapubic cystotomy; implantation of radium; 5507 mg. hours	Death 1 year after operation	Yes	No	Leiomyosarcoma
15	1937	Ashburn and Wollenweber	M	50	Left side of bladder	Not definite	Pain in bladder; small stream; nocturia; burning; no hematuria	Suprapubic cystostomy	Died	Yes	No metastatic deposits found	Leiomyosarcoma

is not mentioned). Three rhabdomyomas have been reported as arising from the trigon or neck of the bladder (Davoni; MacKenzie and Chase; White).

Age.—The general opinion prevails that sarcoma of the bladder occurs relatively more frequently in the very young (children under the age of 5 years) and in persons past 50. A review of the 14 cases of leiomyosarcoma does not tally with this opinion so far as sarcomas in general are concerned. In our series of 14 cases of sarcoma, the lesions in only 3, or about 20 per cent, occurred in children between the ages of 1 and 5 years, whereas there were 10 patients between the ages of 50 and 60. The age distribution is summarized in table 5.

Sex.—In our series of 14 cases, 10 lesions occurred in males and 3 in females. In 1 case the sex of the patient was not stated.

TABLE 4.—*Location of Lesion*

Position of the Tumor	Number of Cases
Posterior wall	5
Anterior wall	1
Right or left lateral	5
All walls	2
Not stated	1
Total	14

TABLE 5.—*Age Incidence in Cases of Leiomyosarcoma of the Urinary Bladder*

Age	Cases
1- 5 years	3
6-10 years	1
11-20 years	1
21-30 years	0
31-40 years	0
41-50 years	2
51-60 years	4
61-70 years	1
70 years	1
Not stated	1
Total	14

Symptoms.—The symptoms varied within wide limits. In 8 of the 14 cases the presence of hematuria was recorded. On the other hand, there were only 2 cases in which its absence was mentioned. In 10 cases there was pain, and in only 2 cases was pain absent. In one-half the cases the symptoms were of less than ten months' duration. Neither clinically nor grossly can leiomyosarcoma be distinguished from other vesical neoplasms. The diagnosis must be based entirely on the microscopic examination.

It is interesting in this connection to note that the preoperative diagnosis in the case first presented was papillary carcinoma and that the diagnosis was so recorded from the first specimen removed at the time of the first cystoscopic examination. The diagnosis made from a second

specimen removed at the time the suprapubic cystostomy was done was recorded as carcinoma, and it was not until careful study of the autopsy specimen was carried out that the diagnosis of leiomyosarcoma was established.

In this connection it is interesting to note that the cystographic appearance of the bladder was normal.

Metastases.—Metastases were rare with sarcoma as well as with leiomyosarcoma. In our series of 14 cases, metastasis occurred in only 1 instance (to the lungs). Autopsies were performed in 6 cases besides our own, and in none of them was metastasis mentioned, whereas in 3 the definite statement was made that metastasis was not present. Implantation or regional recurrence occurred in 2 instances (Mintz and Powell).

Since in most cases leiomyosarcoma originates from the muscle layer of the bladder and thence invades the wall, wide resection of the bladder must be carried out. In spite of radical removal, however, the outcome, with few exceptions, has been death soon after operation. Only 1 patient was alive and well four years and two months after operation, when last heard from in 1932 (Hager and Hunt).

SUMMARY

A case of leiomyosarcoma of the urinary bladder is described.

A summary of 14 such cases is given, in 8 of which the diagnosis was positive and in 6 of which the tumor was described but was not diagnosed as leiomyosarcoma.

Leiomyosarcoma usually occurs in a patient under the age of 12 years or over the age of 45. In most instances the lesion arises from the wall of the bladder.

Metastasis is rare.

Although the tumor in the case reported was enormous, attention should be called to the fact that the cystographic appearance of the bladder was normal. The correct diagnosis was not made until careful study of the autopsy specimen was carried out.

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SPINAL ANESTHESIA

REGULATION OF HEIGHT WITH FRACTIONAL DOSES

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The popularity of spinal anesthesia has undergone various accessions and regressions since its discovery by Corning in 1888. In the hands of such master surgeons as Matas, who was the first in this country to perform an operation employing it, spinal anesthesia proved satisfactory; but for others less experienced and resourceful, it gave unsatisfactory results.

During the second decade of the present century interest in the production of anesthesia by regional injections seems largely to have died out, and the advent of the World War put a temporary embargo on such physiologic experimentation as might have provided better and safer means of administering it. A full decade after the war ended, however, Pitkin brought forward his "controllable" spinal anesthesia, a method which was almost immediately to revolutionize the previous conceptions of the hazards and inconveniences of this particular form of surgical analgesia.

Briefly, the drawbacks had always been (1) a tremendous fall in blood pressure about ten minutes after the administration of the drug employed to induce insensibility and (2) the extremely rapid diffusion of the drug in the spinal canal, which no measure heretofore known had been able to keep under control.

The lowering of blood pressure is, in all probability, due to splanchnic dilatation, which, by causing cerebral anemia, used frequently to prove fatal. Soon after the World War, Labat[1] advocated that the patient be placed in the Trendelenburg position, which was found to reduce the withdrawal of blood from the cerebrum but did not help control the vomiting and retching that intraspinal administration of large doses of anesthetics was almost certain to induce.

Inability to control the extent of the diffusion of the drug in the spinal canal remained an insurmountable obstacle in the way of general

1. Labat, G.: Elimination of the Dangers of Spinal Anesthesia. Am. J. Surg. 5:625, 1928.

employment of this form of anesthesia until Pitkin [2] brought forward his method in 1927. In brief, this consisted of employing a solution of lower specific gravity than that of the spinal fluid, having a viscous consistency which makes it less diffusible, and of placing the patient on a table which could be readily tilted to any desired degree, thus making the angle of the patient's body aid in stopping the ascent of the anesthetizing fluid at the required level of insensibility.

The solution which Pitkin recommended, known as spinocain, is made up of 200 mg. of procaine hydrochloride and 2.2 mg. of strychnine sulfate, dissolved in 14.5 per cent alcohol and sterile water, to which an amyloprolamine combination has been added. This product is a viscous fluid of specific gravity so much less than that of the spinal fluid that it floats on the latter "like the air bubble of a spirit level."

An intradermal injection of a solution containing 1 per cent procaine hydrochloride and 5 per cent ephedrine hydrochloride was made at the site of spinal puncture to render the skin insensible, thus facilitating the introduction of the spinal needle and preventing a too rapid fall in blood pressure. The injection was made with the patient on his side on the level table. When injection was completed the table was immediately tilted to the angle needed to permit diffusion of the anesthetic to the upper limit of the portion of the body on which operation was to be done. For example, with the table tilted so that the patient is in the 15 degree Trendelenburg position, anesthesia will be limited to the perineum and the lower extremities; tilting to the 10 degree level permits diffusion as high as the umbilicus; at 5 degrees insensibility will be complete as far as the lowest ribs, which is as high as it is desirable to operate with this form of anesthesia. A meter designed by Pitkin [2] to be attached to the table made it possible for operator and anesthetist to know precisely how far the anesthetic would rise.

This method of "controllable" anesthesia aimed to make the hitherto decidedly uncertain and hazardous spinal method relatively safe and sure in the hands of experienced and careful operators. My associates and I began to employ it in our clinic soon after Pitkin made his first presentations, so that by 1930 it was possible to report a series of five hundred major operations wherein this form of anesthesia had been used.[3] We had made it a routine in appendectomy, cholecystectomy, gastroenterostomy and nephrectomy. We had also employed it widely when carrying out procedures on the uterus, prostate, rectum and

2. Pitkin, G. P.: Controllable Spinal Anesthesia, J. M. Soc. New Jersey 24: 425, 1927.

3. De Courcy, J. L.: Use of Controllable Spinal Anesthesia in Five Hundred Major Operations, Ohio State M. J. 26:397, 1930.

perineum, as well as in amputations of the lower limbs. The complete relaxation afforded by spinal anesthesia and the absence of straining were particular advantages offered by this method.[4]

Yet despite the great advance of Pitkin's method over anything previously offered for surgical anesthesia, as time went on we found that a number of serious drawbacks attended it. The theory in regard to the nondissemination of the anesthetizing fluid above the desired level was found in practice to fail occasionally. In other words, the anesthesia was not as "controllable" as we would have liked. Also, the postoperative vomiting and retching could not always be eliminated when the quantities advocated by Pitkin were used.

Three years ago we set about improving the method, our chief aim being to limit the ascent of the anesthetizing fluid in the spinal canal and at the same time to minimize the unpleasant after-effects by reduction of the amount of anesthetizing drug needed to produce insensibility to pain in a given area. We experimented to discover how small a quantity of anesthetic agent we could use while still inducing perfect anesthesia and affording time enough for thorough and painstaking surgical procedures. We abandoned spinocain because of its occasionally unfavorable reactions, and now we make use of procaine hydrochloride exclusively, because we have found it less toxic and more uniform in its action.

With the doses which will be mentioned shortly we have had a high degree of satisfaction. The formerly dreaded fall in blood pressure has been absent, while retching and vomiting, which so often impeded us and distressed our patients, have been practically abolished. In a series of 100 cases in which spinal anesthesia was used for operations of various types, vomiting took place but six times. All the operations were on the lower part of the abdomen, for we have found it expedient not to employ general anesthesia for intervention above the umbilicus.[5]

Though this work was aimed primarily at reduction of the dose, the most important thing demonstrated has been the impossibility of abiding by any hard and fast rule. Irrespective of the height which the anesthetizing fluid is required to attain, the same dose should not be used in every case. Fractional dosage, with as little of the anesthetic agent as possible, is of the greatest aid in lessening and eliminating the distressing sequelae once so often witnessed after employment of the earlier methods of applying spinal anesthesia.

Whereas formerly we gave up to 200 mg. in order to perform a prostatectomy or an appendectomy and all too often saw the disagreeable

4. De Courcy, J. L.: Newer Methods of Controllable Spinal Anesthesia: Use of Pitkin's Method in One Hundred Cases, Am. J. Surg. **5**:620, 1928.

5. De Courcy, J. L.: Acute Intestinal Obstruction, Am. J. Surg. **35**:532, 1937.

results of which mention has just been made, we are now performing these same operations satisfactorily when using hardly more than a quarter of the amount of drug once thought necessary. We find that 50 mg. of procaine hydrochloride, mixed with 1 cc. of spinal fluid (barbotized), is sufficient to produce an insensibility which will permit intervention on any tissues located below the course of an imaginary line drawn between the two anteroposterior spines of the ilium. This class of intervention includes suprapubic prostatectomy, replacement of uterine prolapse (if done by the vaginal route), intervention for inguinal hernia and amputation or other operation on the legs. Hemorrhoids can be painlessly removed when no more than 25 mg. of procaine hydrochloride has been injected, and 100 mg. will induce perfect anesthesia for an hour, which is ample time to permit the removal of stones from the kidney and renal pelvis, or complete nephrectomy, as well as cholecystectomy or adrenalectomy.[6] With as little as 75 mg. the anesthesia can be raised above the umbilicus, almost as high as the ensiform cartilage, which allows the performance of such operations as appendectomy and abdominal hysterectomy.

These quantities, it will be observed, are much less than those now being recommended as a routine for spinal anesthesia. For example, King,[7] writing in February 1935, said that workers in his clinic (Pennsylvania Hospital, Philadelphia) dissolve procaine hydrochloride crystals directly in the withdrawn spinal fluid, using 1 cc. of fluid with from 0.05 to 0.10 Gm. of the drug injected in the fourth lumbar space, to produce half hour anesthesia of the perineum, the prostatic bed and the pelvic organs, and (using the greatest amount) one hour anesthesia of the upper pelvic and lower abdominal structures. To this, 50 mg. of ephedrine is routinely added.

In a recently published article, on spinal anesthesia, with special reference to dosage, Atwood[8] reviewed the amounts of anesthetic drugs now in use for spinal injection in different parts of the country. This writer himself, at the advice of William Ross Jr., employs 50 mg. of procaine hydrochloride in a "small amount of spinal fluid" as a routine for urologic procedures lasting from one to one and a half hours. For general surgical work he uses "not over 120 mg. of novocain [procaine] dissolved in two measured cc. of spinal fluid," which gives "a concentration up to 6.16 per cent on injected fluid."

6. De Courcy, J. L.: Technique of Adrenalectomy and Adrenal Denervation, Am. J. Surg. **30**:404, 1935.

7. King, O. C.: Spinal Analgesia: Report of Fifteen Hundred Cases, Ann. Surg. **101**:690, 1935.

8. Atwood, H. S.: Spinal Anesthesia, with Special Reference to Dosage, Northwest Med. **36**:350, 1937.

At the Mayo Clinic concentrations of between 3 and 5 per cent are used, as there procaine hydrochloride is not considered destructive if the concentration is no more than 17 per cent. For appendectomy, Atwood has had satisfactory anesthesia with 60, 70 and 80 mg., but when only 50 mg. was injected the patient experienced severe pain, so that now 100 to 120 mg. is usually employed.

As the perineum is served by nerves from the lowest part of the spinal canal, it follows that the least volume of anesthetic drug will be required to make it insensible. Evans [9] in 1936 reported carrying out in this region operative procedures which caused the patient no pain whatever when only 25 mg. of procaine hydrochloride had been injected. This is a smaller amount than that which we have required for the production of anesthesia of the tissues, even in the perineal region. But for work higher up this same operator used 150 mg. in 2.5 cc. of spinal fluid, and for what may be termed a "high spinal injection" he employed 14 cc. of a 1 : 1,500 solution of procaine hydrochloride.

These citations will serve to demonstrate that the tendency among the majority of operators now is away from large dosage, but I feel that sufficient emphasis has not as yet been laid on the importance of this reduction. During the three years since a consistent effort has been made in our clinic to follow the conservative course which I outlined earlier in this article, there has been a steady improvement not only in the results in our operating room but in the postoperative course of our patients as well, and in the remote results of the operation in cases followed for a long period after operative recovery. We have likewise been able to use spinal anesthesia on patients for whom this would have been absolutely contraindicated at the time when we were employing larger doses and have used it in procedures wherein previously we would not have considered it safe.

As an example the relief of acute intestinal obstruction may be cited. Inhalation methods are not indicated in cases of such obstruction because there is so much danger involved in vomiting or in the aspiration of the gastric content by the unconscious patient. Often such a case does not come under observation until the patient has become profoundly toxic. To a person in this state administration of gas or ether may well prove highly dangerous or even fatal. As I advocated in a previous paper,[5] for these patients it is best to employ 100 mg. of procaine hydrochloride, which is sufficient for a long exploratory incision, or 75 mg. if the site of the procedure is low, as for cecostomy. For some years now I have advocated spinal methods, with careful sedative medication both before and after the actual procedure, for operations of the type of adrenalectomy, which has been satisfactorily performed with 100 mg. of procaine

9. Evans, F.: Anesthesia in Rectal Surgery, Post-Grad. M. J. **12**:345, 1936.

hydrochloride, diluted with 1 cc. of spinal fluid, barbotized only twice. With this small dose vomiting rarely occurs, and the anesthesia remains perfect for almost an hour, ample time for performance of a painstaking operation. The medication consists of ¼ grain (0.0162 Gm.) of morphine sulfate and ¹⁄₁₅₀ grain (0.0004 Gm.) of scopolamine hydrobromide, given three quarters of an hour before operation. An additional safeguard is the administration of ephedrine immediately after injection of the anesthetic and as often while the operation is in progress as the state of the pulse and of the blood pressure would seem to indicate.[6] It is always given intramuscularly. As a routine we allow ten minutes to elapse after injection of the anesthetic before making any attempt to start the surgical incision, the anesthetist meanwhile from time to time making the customary tests for sensibility.

Since adoption of the fractional dose method we have had no fatalities among cases of surgical intervention which could in any way be attributed directly to the effects of the anesthetic. To be sure, we select the subjects for spinal injection with considerable care. We never use the method when the patient is a distinctly "bad risk," even if he presents conditions which strongly contraindicate any form of inhalation technic. In general, we avoid the spinal method in any type of high abdominal work, although I have mentioned that we sometimes use it in cases of acute obstruction of the intestine, when the point of blocking is far down in the canal.

Whether a surgeon should use spinal anesthesia for certain abdominal operations is a matter of personal preference. We have found it better to employ inhalation methods for resection of the stomach and other procedures of that general type, although the administration of 150 mg. of procaine hydrochloride is regularly sufficient to raise the area of insensibility as high up as the nipple line, thus permitting intervention on any structure below the diaphragm. In regard to this Atwood[8] said: "The higher the spinal the more danger of embarrassment of respiration and the more vital becomes the administration of small doses." This strikingly confirms our own experience.

No matter how much confidence the operator has in his ability to control the dose when administering an anesthetic spinally, if he is wise he will not fail to have on hand everything he may need should an emergency arise. A suitable blood donor should always be on call, and the facilities for a transfusion either of blood or of acacia or dextrose should be kept within easy reach. If there is any unavoidable delay, if a traumatic accident occurs or if for any reason, hemorrhage is unduly profuse, such precautions may save not only the patient's life but the operator's reputation, and they may prevent the method of anesthesia from being blamed for results for which it was in no way responsible.

While this method is now called "controllable" anesthesia, it is necessary not to lose sight of the fact that the greater safety of inhalation methods resides largely in the ease with which the anesthetic can be entirely withdrawn as soon as an ill effect on the patient is observed. No injected anesthetic enjoys this advantage. North [10] has truly said, "The great peril of spinal anesthesia lies in the uncontrollable nature of its accidents." The same, of course, is true of rectal and intravenous anesthesia.

For operations which may be done in bed or for relatively simple procedures such as those for hernia or recurrent appendicitis, the spinal method is ideal, since in this type of intervention the patient's general state remains practically the same throughout. In more extensive operations, however, wherein great trauma to the tissues, loss of blood and a general lowering of physical tonus are involved even if an actual state of shock does not supervene, the inflexibility of the spinal method is a grave drawback, for the patient's physical tone is rapidly lowered by hemorrhage and shock, while the amount of anesthetic drug injected remains the same. Consequently, the actual dose to the depleted patient is much higher than it should be, yet one is powerless to withdraw it as one would an inhaled anesthetic. With the inhalation method, one can do even more: by washing out ether or nitrous oxide with oxygen, the anesthetic agent can be removed immediately. This gives the inhalation method a vast advantage over injection of any form of drug.

Against these increased dangers should be set spinal anesthesia's undoubted advantages, chief among which—from the surgeon's point of view—is the complete relaxation it affords. This is of such great aid in operation on the intestinal tract that one is tempted to use the method for those abdominal procedures where perfect relaxation is highly essential to satisfactory work. With sufficient experience and technical skill, spinal or intravenous anesthesia or rectal administration of avertin with amylene hydrate may be employed in abdominal work, even above the umbilicus; yet it must never for a moment be forgotten that these methods of anesthesia are inflexible and that the utmost caution must at all times be employed in their use, especially if the patient has been classed as a "bad risk."

While it is impossible altogether to do away with these inherent dangers, they can be minimized considerably. This, I believe, the method of fractional dosage has done much to accomplish. I am convinced that a systematic use of as little of the anesthetic agent as possible will not only increase the safety of the method but will help abolish the unpleasant after-effects, such as headache, nausea and vomiting, and will

10. North, J. P.: Use and Abuse of Spinal Anesthesia, Ann. Surg. **101**:702, 1935.

give a smoother, more comfortable convalescence than is the lot of the patient operated on under inhalation anesthesia. Both surgeons and specializing anesthetists should labor to perfect themselves in the technic of administration.

Most careful physical examination should be given to every candidate for this type of anesthesia, and the results should be interpreted in terms of the diathesis of the person under consideration. It is not enough to segregate persons with evident abnormalities, such as diabetes or advanced renal impairment. Most of the deaths directly attributable to spinal anesthesia have occurred because some contraindicating factor was overlooked at the preoperative physical examination. The responsibility placed on the surgeon is a great one.

The "safer" anesthetics are also the "easier" ones. Nevertheless, the ever widening employment of spinal anesthesia and the increased demand for it by patients about to undergo operation show that the method is already established in a position of favor from which it would be difficult indeed to dislodge it. Constant care and study for improvement are the only alternative.

CONCLUSIONS

1. Fractional dosage in spinal anesthesia, with as small a dose as is capable of inducing insensibility in the tissues to be operated on, greatly increases the safety and extends the applicability of the method.

2. The height to which the anesthetizing drug rises depends on the dose employed and, to a lesser degree, on the amount of spinal fluid used to dilute it.

3. We have found procaine hydrochloride the most suitable anesthetic agent, with 1 cc. of spinal fluid used to dilute it irrespective of the amount of the drug.

4. In all cases, irrespective of dose or dilution, the effect of the anesthetic will always last for at least an hour. Duration is not affected by the amount of drug administered.

5. "Bad risk" patients should not be subjected to spinal anesthesia; but, other things being equal, hypotension should not be taken as an absolute contraindication to use of the method. If hemorrhage has occurred, however, or if unusual difficulty is anticipated, inhalation methods are safer.

6. When there are no contraindications, spinal anesthesia is used in our clinic for any operation to be performed below the umbilicus.

FRACTURES OF THE UPPER EXTREMITY AND THE SHAFT OF THE HUMERUS

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The purpose of this presentation is to review and evaluate the results obtained in treatment of fractures of the upper extremity and shaft of the humerus by the use of traction with the arm in abduction.[1] Since that treatment has been applied as a matter of routine in the majority of cases, an excellent opportunity is afforded for defining the uses and limitations of the traction-abduction treatment for fractures of the arm. The series includes all the cases in which such fractures were treated in the Beekman Street Hospital, New York, by the various members of the staff from 1929 to 1934 inclusive.

There were 106 fractures of the upper extremity and shaft of the humerus: 17 fractures of the greater tuberosity, 46 fractures of the surgical neck and 43 fractures of the shaft. Fractures of the shaft included 11 fractures of the upper third, 23 fractures of the middle third and 9 fractures of the lower third. Sixty-three, or over 60 per cent, of the 106 fractures involved the head or the surgical neck.

There were 5 deaths, 4 of which were caused by associated injuries in which the humeral fracture played a minor part. The fifth was exceptional and is discussed under the subject of fractures of the greater tuberosity. Amputation was necessitated in 2 instances because of associated injuries. Eight patients were discharged during the course of treatment, against advice or by request.

Two cases of nonunion appear in this compilation. The patients in both were originally treated elsewhere and were operated on for the preexisting nonunion. Exclusive of the cases of nonunion, in 7 cases open reductions were performed and in 1 permission was refused, making a total of 8 cases in which operation was deemed advisable. Judging from the results, 1 other might be added, making a total of 9, or 8.4 per cent. All of the open reductions were performed because of persistent malposition, and it is probable that the fractures in some cases would have failed to unite without open reduction.

In accordance with general experience, the proximity of the fracture to the shoulder joint varied directly with the age of the patient.

The percentage of fractures requiring open reduction in any series will depend on two factors, the proficiency of the surgeon in perform-

1. Blake, J. A., and Bulkley, K.: The Treatment of Fractures of the Extremities by Means of Suspension and Traction, Surg., Gynec. & Obst. **26**:245 (March) 1918.

ing closed reduction and the degree of anatomic reduction regarded as adequate. In this connection it is interesting to note that all displacements of the neck and upper third of the shaft which were treated by open reduction, with 1 exception, can be duplicated by cases in which the fracture was successfully reduced by closed reduction. The exception was a lateral displacement of the distal fragment in fracture of the upper

Fig. 1 (case 77).—*A,* fracture of the surgical neck of the humerus. The roentgenogram was taken on the patient's admission to the clinic, with the arm *in* adduction (anteroposterior view). Note the angulation; the apex of the angle *is* lateral. *B,* arm in abduction. Note the reversal of the angulation.

third of the shaft, of which there were 2 examples. It is also noteworthy that the fractures were transverse in 8 of the 9 cases in which open reduction was done, in the case in which the patient refused opera-

tion and in both cases in which the patients were admitted for nonunion. This corresponds with the well recognized fact that traction is least effective for transverse fracture and that such a fracture is the fracture which most frequently results in nonunion. A few years ago it was felt that because of the small number of open reductions performed in this clinic the opportunity did not permit any one surgeon to acquire proficiency in operative measures, and since then all such operations have been assigned to one member of the staff. The improvement in operative results has amply justified this change in regimen.

Thirty-three, or approximately one third, of the fractures were the result of traffic injuries. Twenty-four patients suffered severe associated injuries. As has been mentioned, associated injuries resulted in 4 deaths.

There were 3 pathologic fractures, all of which healed without incident. No fracture in this series resulted from a neoplasm.

Callus was noted roentgenologically at four weeks and clinical union at between five and six weeks on the average. It has been the rule to hospitalize patients who are being treated by traction until clinical union has occurred.

It is to be noted that fracture of the greater tuberosity was more than twice as frequent on the right side, whereas the incidence of other fractures was nearly reversed. This inconsistency might be explained by the fact that the former usually resulted from indirect injury and the latter more often from direct violence. In indirect trauma the more efficient arm is instinctively used to ward off injury, and the less expert arm is more vulnerable to direct trauma.

Seven patients had compound fractures, and all the fractures occurred in the shaft. For only 1 of these was débridement done, and amputation was later required because of associated injuries (thrombosis of the axillary artery and tear of the brachial plexus). Infection played no part in the results, all the fractures healing without infection. The number of compound fractures does not warrant a discussion of their treatment. I should like to call attention, however, to the fact that this series presents no evidence for justification of the more radical active treatment of compound fracture which at present seems to be gaining ascendancy. I believe that compound fracture of the lower extremities should be treated more radically than compound fracture of the upper extremities because of the increased danger of infection.

Incomplete palsy of the radial nerve was noted in a few instances. Operative relief was required in only 2 cases; the patient in 1 was admitted for nonunion. Open reduction was indicated in both, irrespective of the involvement of the nerve. Permanent impairment of the radial nerve did not occur in any case in this series.

The impression is widespread that disability of the shoulder joint is more marked than disability caused by similar fractures of the hip joint.

I believe that this relative discrepancy is more apparent than real. The range of motion of the upper extremity is so much greater that a proportionate loss of motion is more apparent. Loss of function of the shoulder is more noticeable to the patient because the extreme range of motion at the shoulder is employed more frequently by elderly persons than is that of the hip. Except in fractures of the head and surgical neck, motion at the scapulohumeral joint is commonly regained completely. One fracture of the surgical neck and head showed complete

Fig. 2 (case 10).—Fracture of the surgical neck of the humerus, lateral view. There is angulation, with the apex of the angle anterior. The coracoid process is seen projected forward to the right; the acromion process can be seen superimposed on the head.

loss of function of the scapulohumeral joint. This case is discussed in the present paper.

The Blum adaptation of Russell traction has been used in 8 cases of this series. My experience with this method is not sufficiently extensive to justify extended comment.[2] However, in addition to permitting

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2. Blum, L.: Double Pulley Traction in Fractures of the Shaft of the Humerus, J. A. M. A. **101**:1953 (Dec. 16) 1933.

abduction and external rotation, it allows the application of considerably more traction, since the entire forearm and wrist gives a more effective surface for pull than does the upper part of the arm, with the addition of the accessory pull at the elbow joint. If still more traction is desired, a Kirschner wire may be inserted through the lower end of the humerus or the olecranon and skeletal traction applied directly to the humerus. Skeletal traction was employed only twice in this series.

Fig. 3.—*A*, fracture of the surgical neck and head of the humerus, with complete medial displacement and overriding. The roentgenogram was taken on the patient's admission to the hospital. *B*, same fracture four weeks after reduction (lateral view). There is anterior displacement of the shaft of about 50 per cent. *C*, same fracture eight weeks after reduction (anteroposterior view). Callus is evident.

Fracture of the Greater Tuberosity.—There were 17 fractures of the greater tuberosity alone, 12 occurring as complications of dislocations

TABLE 1.—*Fractures of the Greater Tuberosity*

Number	Age of Patient	Sex of Patient	Arm	Compound or Simple Fractures	Dislocation	Treatment	Duration of Traction	Duration of Hospitalization	Associated Injuries Other Than Dislocations	Follow-Up	Result		Comment
											Anatomic	Functional	Result at discharge
11	49	M	R	S	D	Closed reduction; traction 6-8 lb. (2.7-3.6 Kg.)	14	14	0	0	4	4	
12	44	M	R	S	D	Closed reduction; immobilization	..	5	0	0	..	..	
13	30	F	R	S	D	Closed reduction; immobilization	..	3	0	0	..	..	Left against advice
14	64	M	R	S	0	Sling; active motion	..	16	0	0	..	..	Remained for diabetic treatment
31	48	M	L	S	D	Closed reduction; immobilization	..	16	Cerebral concussion	0	..	..	
34	50	M	R	S	0	Sling; active motion	..	20	0	5 yr.	4	3	Repair of hernia
35	72	F	R	S	0	Sling; active motion	..	15	Cerebral concussion	4 mo.	4	3	
36	45	F	R	S	D	Closed reduction; traction 3-4 lb. (1.3-1.8 Kg.)	26	31	0	0	..	..	
57	57	M	R	S	D	Closed reduction; traction	17	20	0	Died	Died	..	Hematogenous infection of shoulder (B. mucosus capsulatus)
57	58	F	L	S	D	Closed reduction; immobilization	..	2	0	0	..	..	
59	51	F	R	S	D	Closed reduction; traction	10	20	0	1½ yr.	4	4	Hypertension; obesity
70	46	M	L	S	D	Closed reduction; traction	13	19	0	6 mo.	4	3	
86	61	M	R	S	D	Closed reduction	..	8	0	0	..	..	Hypertension; chronic nephritis; chronic otitis media; arteriosclerosis; bilateral hernia
88	39	M	L	S	D	Closed reduction; traction of 10 lb. (4.5 Kg.)	25	31	0	1½ yr.	1	4	Fracture of surgical neck of same arm 8 weeks later
89	44	M	L	S	0	Traction	23	23	Burn of arm and hand	0	..	..	
91	26	M	R	S	D	Closed reduction; traction	9	11	0	0	..	..	
93	49	M	R	S	0	Sling; active motion	..	32	Fracture of tibia and shaft of fibula	0	..	..	

of the head of the humerus. Displacement in every case in which it occurred was associated with dislocation, and reduction of the dislocation resulted in satisfactory reduction of the displacement. In no case was open reduction indicated. A fracture of this type should be looked for in all cases of dislocation of the humerus.

There was 1 death in this group, the only death in the entire series in which the humeral injury was an important factor. The patient was a man aged 57, who had been suffering from enteritis for several years. He had fallen on his right shoulder two days before admission. On admission he had a subcoracoid dislocation and a fracture of the greater tuberosity, with marked displacement. A closed reduction was performed with the patient under ether anesthesia. He was suffering from
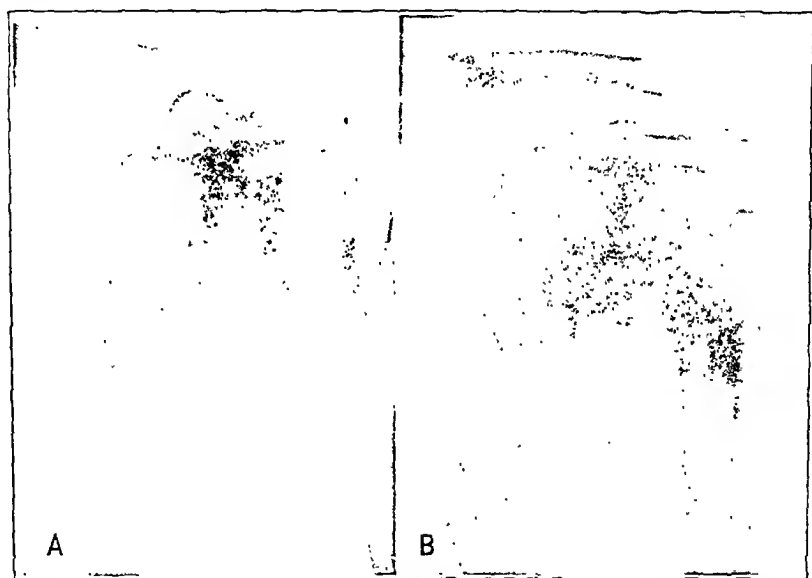
Fig. 4 (case 2).—*A*, fracture of the surgical neck and head of the humerus and subcoracoid dislocation of the shoulder after reduction. Note the portion of the head which has remained in a subcoracoid position. *B*, same fracture after four months. Note the reformation of the neck to the subcoracoid portion of the head.

diarrhea and had a septic temperature, with leukocytosis. Thirteen days after his admission to the hospital, fluid was found in the shoulder joint and was aspirated. The following day through and through drainage of the joint was instituted, and the patient died five days later of sepsis. Cultures of the fluid showed Bacillus mucosus capsulatus. Cultures of the blood were consistently sterile. It is surprising that such experiences are so rare. If open operation had been performed, the surgeon would have borne the onus of infection and death.

The follow-up results, obtained in only 35 per cent of cases, are too incomplete for satisfactory analysis. However, 2 A4-F4 results and 1

TABLE 2.—*Fractures of the Surgical Neck of the Humerus*

Number Patient	Age of Patient	Sex of Patient	Arm	Simple or Compound Fracture	Treatment	Duration of Traction	Duration of Hospitalization	Associated Injuries	Follow-Up	Result		Comment
										Anatomic	Functional	
1	68	F	L	S	Blake traction, 6-8 lb. (2.7-3.6 Kg.)	45	58	0	4½ mo.	4	3	Abduction 90°
2	69	M	L	S	Closed reduction	..	1	Dislocation of shoulder	5 mo.	2	2	No motion in scapulo-humeral joint
5	64	M	R	S	Blake traction, 6-7 lb. (2.7-3.2 Kg.)	38	50	0	9 mo.	4	3	Abduction 135; internal rotation 45, external rotation 45; Colle's fracture 2 mo. before
6	56	F	L	S	Blake traction 6 lb. (2.7 Kg.)	28	32	0	1 yr.	4	3	Abduction 170; slight limitation internal rotation (left)
8	42	F	L	S	Blake traction 4-6 lb. (1.8-2.7 Kg.)	35	42	0	……	4	3	Open reduction 18th day;
10	49	M	L	S	Closed reduction; operation; traction	17	51	0	6 mo.	4	3	abduction 150°, rotation complete
15	65	M	L	S	Blake traction 5-6 lb. (2.3-2.7 Kg.)	39	43	0	10 mo.	4	4	Plaster splen in abduction; left against advice
16	48	F	L	S	Blake traction 6 lb.; Kirschner wire; closed reduction	..	..	0	……	..	..	Transferred; alcoholism
17	58	M	L	S	Closed reduction; Blake traction 6 lb. (2.7 Kg.)	4	5	0	0	..	..	Transferred day of admission
18	51	M	L	S	Blake traction 10 lb. (4.5 Kg.)	5	5	……	……	4	3	At discharge
19	65	M	L	S	………	41	43	0	0	..	..	Left against advice; airplane splint
20	32	M	R	S	Blake traction 6-8 lb. (2.7-3.6 Kg.)	15	16	0	0	4	4	
21	68	M	L	S	Blake traction 8 lb. (3.6 Kg.)	12	13	Concussion fr. nose	4 yr.	4	3	Fell 10 feet; shock; diabetes
22	26	F	L	S	Blake traction 3 lb. (1.3 Kg.)	..	44	Fracture of left clavicle, right fibula, middle phalanx left 5th finger	7 mo.	4	2	
23	65	M	L R	S S	Active motion / Active motion							
25	15	M	L	S	Blake traction	17	21	0	4 mo.	4	4	Epileptic
26	65	M	R	S	Active motion	..	4	0	4 mo.	4	3	Arthritis of knees; treatment in clinic prevented
27	34	M	R	S	Blake traction 5-10 lb.	19	27	0	0	..	3	
28	41	F	L	S	Blake traction 5-7 lb. (2.3-4.5 Kg.)	43	50	0	3 mo.	4	4	
29	62	M	L	S	Blake traction 6-8 lb. (2.3-3.2 Kg.)	27	29	0	5 yr.	..	..	Motion of shoulder excellent on discharge
30	65	M	L	S	Blake traction 6-8 lb. (2.7-3.6 Kg.)	35	38	0	0	4	4	
33	50	M	L	S	Blake traction 5 lb. (2.3 Kg.)	28	32	0	3 mo.	4	4	

No.	Age	Sex	Side	S	Treatment			Associated injury				Remarks
33	67	F	R	S	Blake traction	60	81	Fracture of external condyle (right); head of radius (right); dislocation of elbow (right) — 0	......	..	..	Treatment of elbow complicated by difficulty with retention; aligned release
62	11	M	R	S	Closed reduction; Blake traction 5-10 lb. (2.3-4.5 Kg.); open reduction	0	53	0	6 mo.	1	1	Lateral displacement and angulation; null
67	40	F	R	S	Closed reduction; Blake traction 5-10 lb. (2.3-4.5 Kg.); open reduction	20	72	0	1 yr.	5	4	Lateral displacement and angulation; null
68	18	M	L	S	Sling; active motion	..	90	Fracture of 11th and 12th left ribs, left clavicle, Colles left; pelvis; hemothorax left; contusion left kidney — 0	0	.	..	Slight limitation of abduction and external rotation at discharge; sailor; fell 40 feet in hold of ship
69	57	M	L	S	Blake traction 8 lb. (3.6 Kg.)	..	..	Fracture of skull; concussion — 0	0	..	..	
73	41	F	R	S	Closed reduction; Blake traction 11 lb. (5 Kg.)	40	44	Fracture of right ulna; dislocation of right radius — 0	5 mo.	4	4	Closed reduction of forearm
74	41	M	L	S	Closed reduction; Blake traction	46	50	0	5 mo.	4	3	Uncooperative
75	13	M	L	S	Blake traction 5-7 lb. (2.3-3.2 Kg.)	23	23	0	5 mo.	4	4	Epiphysial separation
76	40	M	L	S	Blake traction 5 lb. (2.3 Kg.)	10	37	0	1 yr.	1	1	Bilateral hernia repair
77	37	M	R	S	Blake traction 6-10 lb. (2.7-4.5 Kg.)	28	30	0	10 mo.	4	3	Limited rotation
78	17	M	R	S	Blake traction 10 lb. (4.5 Kg.)	18	23	0	1 yr.	4	4	
80	68	M	R	S	Sling; active motion	..	31	0	0	..	..	Syphilis of central nervous system, cord, bladder
81	38	F	L	S	Blake traction 15 lb. (7.3 Kg.)	30	31	0	0	..	..	Abduction complete on discharge
85	65	M	R	S	Blake traction 5-10 lb. (2.3-4.5 Kg.)	22	36	0	4 mo.	4	4	
90	44	M	L	S	Blake traction 15 lb. (7.3 Kg.)	37	39	0	0	..	..	Fracture of greater tuberosity of same arm 2 mo. before
92	93	M	L	S	Blake traction 5-10 lb. (2.3-4.5 Kg.)	31	33	0	3 mo.	4	4	Uncooperative; anxiety neurosis
96	49	M	L	S	Closed reduction; traction (Hiun) 5 lb. (2.3 Kg.)	5	18	0	3 mo.	1	3	Old fracture of skull; senile; complete displacement; refused operation A.O.R.
97	73	M	L	S	Blake traction 8-12 lb. (3.6-5.4 Kg.)	20	26	0	0	..	..	
99	57	M	L	S	Blake traction 0 lb. (2.7 Kg.)	30	40	0	0	..	..	
100	35	M	L	S	Blake traction 7-10 lb. (3.2-4.5 Kg.)	26	39	0	0	..	..	
101, 102	61, 67	M, F	R, L	S, S	Sling; active motion	..	7, 6	0, 0	0, 1 yr.	..	3	Injury 3 weeks old 90 abduction; other motions complete
104	21	F	L	S	Blake traction 3½ lb. (1.5 Kg.)	41	40	0	0 mo.	4	4	Radial paresis; temporary

A4-F3 result, as well as one A4-F4 on discharge were obtained by use of the Blake board with the arm in abduction from ten to twenty-five days. The other 2 patients who showed A4-F3 results were treated with sling and active motion, and the fractures were not complicated by dislocation. These results seem to favor abduction treatment.

Hospitalization varied from two to thirty-two days, with an average of approximately seventeen days. The longer periods were required because of associated injuries or other conditions. In addition to dislocations there were 2 cerebral concussions, 1 fracture of the tibia and the fibula (upper third) and a severe rope burn of the hand and arm in an eighteen story slide. One patient remained for a hernia operation, 1 for diabetic treatment and 1 on account of the hematogenous infection mentioned. One patient suffered a fracture of the surgical neck of the humerus of the same arm while still under treatment in the clinic.

There were no compound fractures in this group.

Fracture of the Surgical Neck.—According to Stimson's classification, only 1 of these fractures was a true fracture of the anatomic neck of the humerus and that was an epiphysial separation of the upper humeral epiphysis, the only epiphysial separation in this series. On the other hand, many of the fractures involved the anatomic neck through most of its extent. Of the 46 so-called fractures of the surgical neck, 14 also involved the greater tuberosity or the head of the humerus, or both. One fracture was bilateral. Only 1 was complicated by dislocation of the head of the humerus.

The ages of the patients varied from 11 to 73 years. The average was 52½. On the whole, therefore, the patients formed an unfavorable age group for function and union.

In the 17 recorded cases callus was present after from seventeen to thirty-eight days, an average of twenty-seven days. Union occurred in from twenty-one to seventy-two days, an average of thirty-seven days. Union was obtained in all cases.

There were no pathologic fractures in this group. Eight patients had severe associated injuries. There were no deaths.

There were no compound fractures. Fractures involving the humeral head and neck are unlikely to be compounded because of the surrounding muscles and tendons.

Fractures of the surgical neck frequently appear impacted on roentgen examination. Firm impaction is the exception and should not be considered when gross displacement is present. Lateral as well as anteroposterior roentgenograms are essential in determining impaction and displacement, a determination which may be difficult because of the obliquity of the fracture line and rotation of the head. There is no typical displacement of either fragment and the weight of the extremity or the fracturing force is the most important factor in causing displacement. For example, on admission there is generally angulation with the

apex of the angle lateral, and after abduction, even though gradual, the angulation is commonly reversed, the apex of the angle being medial. This is true of most of the cases in this series in which roentgenographic diagnoses of impaction had been made. Angulation with the apex anterior is common and usually is not influenced by abduction or traction. In cases with overriding and complete displacement the fracture may be reduced by closed reduction or by skeletal traction. Cutaneous traction alone is not effective in reducing overriding in fractures of the
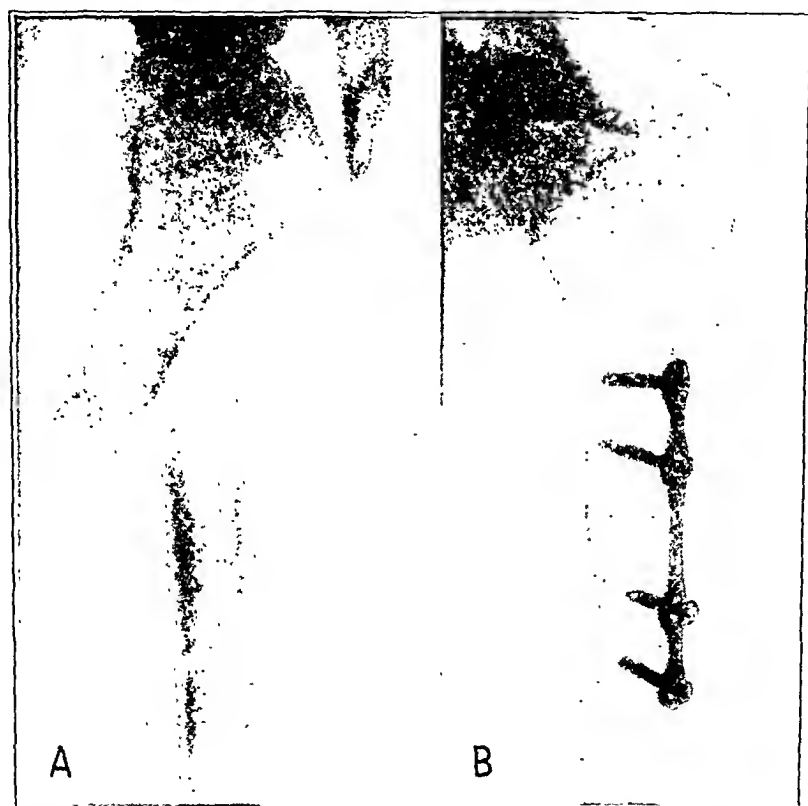
Fig. 5 (case 98).—*A*, fracture of the shaft of the humerus (upper third) with complete lateral displacement and overriding. There were no instances of successful closed reduction of displacements of this type. *B,* same fracture six months after open reduction.

surgical neck. Open reduction was done for 3 patients and refused by 1.

In 1 case (case 2) the injury was complicated by a dislocation and fracture of the humeral head. After reduction a portion of the head remained subcoracoid. This reunited to the shaft and prevented motion at the shoulder joint. It was recognized that this fragment should be removed or reduced, but because of the patient's age (69) and poor general condition no operation was performed. This was the only known

case in which the functional result was poor. It was the only instance of a fracture of the humeral neck complicated by dislocation. Osseous deformities were common roentgenographically, but clinically they were not evident, nor were they known to be responsible for functional disability in any of these cases, other than that aforementioned.

The patient in 1 case (case 97), with a transverse fracture and complete medial and anterior displacement with overriding which was not improved by traction and closed reduction, refused operation. Without operation nonunion was anticipated, but no follow-up was obtained.

Three fractures were treated by open reduction. Two were displaced laterally and anteriorly with the angulation apex medial and were maintained by a nail. The position of one of these (the patient was a child) was not improved. Both had A4-F4 results (cases 62 and 67). In the third case exploration was done on the eighteenth day and showed beginning union and fair position. The fracture was not influenced by the operation. This case was followed for six months and showed an A4-F4 result.

Fracture of the Upper Third of the Shaft.—There were 11 cases of fracture of the upper third of the shaft. The youngest patient was 11 years of age, the oldest 72. The average age was 42. There were 9 male and 2 female patients. Three fractures were compound and the others simple.

One was reduced and treated in plaster. Five were treated by traction, 1 with the Blum apparatus and the rest with Blake board. Two were treated by open operation with the Sherman plate.

In 1 case of compound fracture débridement was done and amputation was later performed because of thrombosis of the axillary artery, beginning gangrene and a tear of the brachial plexus. There were 2 additional compound fractures, both caused by gunshot wounds, which were treated conservatively and which healed without incident.

There were 2 deaths. Both patients died in less than twenty-four hours, of severe associated injuries, never recovering from the initial shock.

One fracture was pathologic; it was caused by a solitary bone cyst occurring in a child of 11. The cyst had largely disappeared three months after the fracture.

In 1 case there was delayed union (fifty-four days) as a result of poor apposition, treated by Blake traction. Open operation was seriously considered in this case but was deferred as crepitus was easily elicited. A follow-up after twenty months showed an A4-F4 result.

In 1 patient there was overriding with lateral displacement of the distal fragment. Traction and closed reduction failed to improve the position. A Sherman plate was applied. The patient was transferred to another hospital the day after operation, as he had an alcoholic

TABLE 3.—*Fractures of the Upper Third of the Humerus*

Number	Age of Patient	Sex of Patient	Arm	Simple or Compound Fracture	Treatment	Duration of Traction	Duration of Hospitalization	Associated Injuries	Follow-Up	Result		Comment
										Anatomic	Functional	
21	59	M	R	S	Closed reduction; Blake traction 7-11 lb. (3.2-5 Kg.)	39	42	0	Died	3	1	½" short
38	48	F	R	S	Other injuries	..	..	Concussion; fracture of clavicle, right; ribs 1-10 right, 1-5 left; laceration right lung and pericardium; hemothorax right and left	Died	..	..	Lived less than 21 hours
40	20	M	R	S	Closed reduction; Blake traction; open reduction	8	10	0	......	..	..	Sherman plate; good reduction; transferred; delirium tremens
53	39	M	L	O	Blake traction 7-10 lb. (3.2-4.5 Kg.)	37	40	Gun shot (2)	0	..	..	No infection
59	40	M	L	O	Débridement; amputation; late traction (Kirschner)	..	..	Gangrene of forearm and hand	......	..	..	Amputation
60	72	M	L	S	Other injuries	..	1	Fracture of pelvis, ribs (left)	Died	..	..	Bronchopneumonia; lived 20 hours
63	11	M	L	S	Plaster splen	..	21	Solitary bone cyst	3 mo.	4	4	Cyst cured by fracture; pathologic
72	71	F	L	S	Plaster splen 5-7 lb. (2.3-3.2 Kg.)	35	38	0	0	4	..	
81	53	M	L	S	Plaster splen	51	54	0	2 yr.	4	4	Delayed union; operation considered
98	28	M	L	S	Plaster splen 4-6 lb. (1.8-2.7 Kg.); closed reduction; open reduction	12	33	Fracture of left scaphoid minor and radial styloids; dislocation carpus	1½ yr.	4	4	Sherman plate
103	39	M	L	O	Blunt traction 4 lb. (1.8 Kg.)	41	47	Gun shot	1 yr.	4	4	No infection

TABLE 4.—*Fractures of the Middle Third of the Shaft of the Humerus*

Number Patient	Age of Patient	Sex of Patient	Arm	Simple or Compound Fracture	Treatment	Duration of Traction	Duration of Hospitalization	Associated Injuries	Follow-Up	Result		Comment
										Anatomic	Functional	
3	40	M	L	S	Blake traction 6-7 lb. (2.7-3.2 Kg.)	81	102	Fracture of pelvis, laceration of urethra	7 mo.	3	3	Delayed union; traction discontinued too soon; angulation recurred
4	13	M	R	S	Blum traction 3-3½ lb. (1.3-1.5 Kg.)	37	40	0	1 yr.	4	4	
7	14	M	R	S	Blum traction 2-3 lb. (0.9-1.3 Kg.)	27	32	0	1 yr.	4	4	Slight limitation of pronation of elbow and second finger; plating of radius
9	43	M	R	S	Blake traction 5-7 lb. (2.3-3.2 Kg.)	56	64	Complete fracture of right radius and right ulna, 2d metacarpal (right)	1 yr.	4	4	
41	1½	M	R	S	Closed reduction; plaster	..	17	0	1 yr.	4	4	Kept in hospital for convulsions
45	20	M	L	S	Blake traction 8-10 lb. (3.6-4.5 Kg.)	41	45	0	5 yr.	4	4	
46	47	M	L	S	Blake traction 10-12 lb. (4.5-5.4 Kg.); closed reduction	36	42	Right Colles fracture	1 yr.	4	4	Still under treatment
47	57	M	L	S	Blake traction 8-23 lb. (3.6-10.4 Kg.)	35	40	0	3 mo.	4	3	Abduction 165?
48	40	M	R	C	Blake traction 8 lb. (3.6 Kg.)	37	44	Laceration of right hand and forearm	5 yr.	3	3	
49	56	M	R	S	Blake traction 8-10 lb. (3.6-4.5 Kg.)	39	44	0	4 mo.	4	4	Pathologic fracture; osteitis deformans
51	25	M	R	S	Blake traction 6-8 lb. (2.7-3.6 Kg.)	34	36	0	1 yr.	4	4	
54	54	M	L	C	Other injuries	..	1	Concussion; fracture pelvis, left; calcaneus, dislocation 1st metatarsal	Died	..	..	Lived 7 hours
63	40	M	R	S	Blake traction 5-7 lb. (2.3-3.2 Kg.)	36	49	0	2 mo.	4	3	
64	51	M	L	S	Plaster spica	..	44	0	9 mo.	4	4	Letter; hospitalized because of inability to use crutches
65	31	M	L	S	Blake traction 7 lb. (3.2 Kg.)	6	6	0	0	..	..	Good position in traction; left against advice; psychosis
66	27	M	L	S	Blake traction 5-7 lb. (2.3-3.2 Kg.)	27	35	0	0	..	..	Original treatment elsewhere; nonunion
71	56	M	R	S	Open reduction; tibial graft	..	14	0	0	..	..	Temporary radial paresis; Sherman plate; removed 2 mo.
79	40	M	L	C	Blake traction 8-10 lb. (3.6-4.5 Kg.); open reduction	13	47	0	10 mo.	4	4	A4-F4 result on discharge
82	11	M	L	S	Blake traction 10 lb. (4.5 Kg.)	29	31	0	0	4	4	No operation
83	16	M	L	C	Blake traction 5-10 lb. (2.3-4.5 Kg.)	28	30	Compounded from within	15 mo.	4	4	
87	27	M	L	S	Blake traction 12 lb. (5.4 Kg.)	35	71	Laceration of forearm with infection	1 yr.	4	4	
95	66	M	R	S	Blum traction 4-7 lb. (1.8-3.2 Kg.)	52	57	0	5 mo.	4	4	
103	41	M	R	S	Blum traction 2-7½ lb. (0.9-3.4 Kg.)	33	40	0	5 mo.	4	3	

TABLE 5.—*Fractures of the Lower Third of the Shaft of the Humerus*

Number of Patient	Age of Patient	Sex of Patient	Arm	Simple or Compound Fracture	Treatment	Duration of Traction	Duration of Hospitalization	Associated Injuries	Follow-Up	Result Anatomic	Result Functional	Comment
32	39	M	R	S	Amputation	..	..	Compound crushing fracture radius and ulna at elbow	.....	..	..	Amputation at site of fracture
42	35	M	R	S	Blake traction 8 lb. (3.6 Kg.)	59	72	Right hemothorax; emphysema; fracture right clavicle	6 mo.	4	1	
43	12	M	L	S	Blake traction 5-8 lb. (2.3-3.6 Kg.)	29	33	0	0	..	..	At-Ft result at discharge
41	51	M	R	S	Other injuries	..	1	Fracture of tibia and fibula right; tibia and fibula left; ribs right 3-10; hemothorax; rupture of liver and spleen	Died	..	..	Lived 11 hours
60	48	F	L	S	Blake traction 10-12 lb. (4.5-5.4 Kg.)	38	42	0	0	..	..	
62	25	M	L	S	Blake traction; open reduction	10	21	0	2 mo.	3	3	Limitation of motion at elbow
65	27	M	L	S	Blake traction 10-12 lb. (4.5-5.4 Kg.)	41	16	Fracture of skull; laceration of brain; 1st dorsal vertebra	0	..	..	
68	39	M	R	S	Open reduction 11/31/28; open reduction 5/8/29	..	..	Nonunion; refracture	.....	..	..	(1) Freeing radial N.; bone chips; (2) Inlay tibial graft, union
91	30	M	L	S	Blake traction 5 lb. (2.3 Kg.)	37	42	'T' fracture; intercondylar	1 yr.	4	3	

psychosis. The reduction obtained was satisfactory. There was no follow-up (case 40).

The other open operation with plating was necessitated by overriding and persistent lateral displacement of the distal fragment. In addition to the fracture of the humerus, the patient suffered a fracture of the scaphoid, a fracture of the radial and ulnar styloid processes and a posterior dislocation of the carpus of the radioulnar joint of the same extremity. Immediate closed reduction of the wrist was performed, together with prolonged immobilization as advocated by Bohler. An A4-F4 result was obtained and the patient was able to continue his work as an expert typist (case 98).

Fracture of the Middle Third of the Shaft.—There were 23 fractures of the middle third of the shaft. The youngest patient was 1 year of age and the oldest 66; the average age was 36. All were male. In 11 cases the fracture involved the right arm and in 12 the left. Two patients were treated by closed reduction and plaster spicas, and 18 by balanced traction (14 by the Blake apparatus and 4 by Blum's method). Open reduction was done for 2 of these fractures, 1 of them being an old fracture with nonunion; in 1 case (case 71) a sliding bone graft from the tibia was used; in the other (case 79), the Sherman plate was employed. Two patients were discharged at their own request.

There were 2 pathologic fractures, 1 caused by an old poliomyelitic infection and the other by osteitis deformans.

There was 1 death, seven hours after admission, from associated injuries.

Traction was maintained for the longest period (eighty-one days) in case 3. The patient was taken out of traction too soon, with resulting angulation, as union was not solid. Therapy in each case must be individualized. Standardized treatment will result in many failures.

There were 4 compound fractures. Two were compounded from without, 1 occurring in the patient who died. The other 2 were compounded from within. The 3 survivors were treated conservatively, and the fractures healed without infection.

Fourteen patients were treated with Blake board traction; of these, 7 presented A4-F4 results, 2 presented A4-F3 results, 1 presented an A4-F4 result on discharge and the results for 2 are unknown.

Four were treated with Blum board traction; of these, 3 presented A4-F4 results and 1 presented A4-F3 result.

Two were treated with closed reduction and plaster spica. Both presented A4-F4 results.

Two were treated with open reduction; of these, 1 presented an A4-F4 result. The result for the other is not known.

There was 1 death.

Fracture of the Lower Third of the Shaft of the Humerus.—There were 9 fractures involving the lower third of the shaft. Eight patients were male and 1 female. Five fractures resulted from traffic injuries, 2 from falls on the street, 1 from a fall from a height, and 1 from other injury. Four were on the right and 5 on the left side. None were compounded. Five were treated by traction (4 by Blake and 1 by Blum traction). One was an old fracture with nonunion and paralysis of the radial nerve, which had been operated on elsewhere with retention by kangaroo tendon. Two operations were performed, the first freeing the radial nerve and freshening the bone ends. Seven months later the bone was refractured and plated at a second operation. There was no nerve paralysis and union was obtained. The follow-up period was three months.

In 1 case amputation was done on admission because of compound crushing fracture of the forearm with involvement of the elbow joint.

Four patients had associated injuries; of these, 1 died eleven hours after admission.

Open reduction was performed in 1 case in addition to the case of nonunion, the fragments being retained with a Sherman plate. Union was obtained with moderate deformity, and flexion of the forearm was limited to 90 degrees.

Of the 5 cases in which traction was used the results of treatment in 2 are unknown, except that union was present on discharge.

Two patients treated with Blake traction presented A4-F4 results.

One patient with a T fracture treated by Blum traction showed an A4-F3 result after one year.

CONCLUSIONS

Fracture of the surgical neck frequently results in partial loss of abduction and external rotation. From a review of cases of this condition it is obvious that traction-abduction is not effective in overcoming anatomic displacement, and indeed often results in increased deformity, i. e., angulation with the apex medial. From the point of view of displacement it is obviously preferable to place the distal fragment in alinement with the proximal fragment, which would eliminate abduction at 90 degrees in the majority of cases. The only valid argument for traction-abduction for fracture of the surgical neck (excluding fracture in which the upper fragment is abducted) is the preservation of abduction and external rotation. I have not had sufficient experience with other methods to answer that question finally, but I believe that the difference in results is not sufficient to justify its continuance, except where it is warranted by the position of the upper fragment. I propose to try a modification of the Henderson splint with an adjustable hinge for varying degrees of abduction and ambulatory treatment in such cases. In addition to the advantages of mobilization, it would greatly reduce the expense both to the patient and to the hospital. In cases of

fracture of the surgical neck, nonunion is so rare as not to deserve consideration in the choice of treatment.

Nonunion is an important consideration in cases of fracture of the shaft. W. C. Campbell [3] wrote that "delayed union and non-union occur more often in fractures of the shaft of the humerus than in any other long bone." Von Bruns reported that of 1,274 ununited fractures, 376, or 30 per cent, were fractures of the humerus, and of 681 cases of pseudarthrosis, 226, or 33 per cent, involved the humerus. Codvilia, Cuneo and Sutro found 32 per cent of cases of pseudarthrosis of the humerus as against 13 per cent of cases in which the condition involved the tibia.[4] Including 41 cases reported by Colp and Findlay during 1926 and 1927 there have been no known instances of nonunion in fracture of the shaft of the humerus in 82 patients treated primarily at the Beekman Street Hospital.[5] This would indicate that for fracture of the shaft traction-abduction treatment is an effective method of immobilization.

It is especially successful for fracture of the middle third and to a slightly less extent for fracture of the upper third. Results have been least satisfactory for the lower third, but they are based on comparatively few cases. Fracture of the lower third of the shaft is difficult to treat by any method. It would seem that for such a fracture, when anatomic reduction is not promptly obtained by traction, open operation should be resorted to. It is evident, however, that in the presence of a comminuted fracture or a T fracture the operator's skill will be taxed to the utmost to avoid impairment of the elbow joint.

The use of traction should be combined with closed reduction, and when reduction is successful osseous union should occur. The addition of closed reduction is particularly necessary for transverse fractures. Delayed union will result in nonunion if immobilization is not continued until fusion occurs. Its duration should allow for individual variation in the length of the period of healing.

It is desirable that a prompt decision should be made whether to persist with closed methods or resort to open operation. It should be possible within a week to arrive at such a decision. Some of my results with open reduction would have been better if this decision had been made earlier. It makes operative treatment easier and results in a shorter period of disability and a better functional result for the patient. Calcification of callus and the late softening of the cortices of the bones due to decalcification vitiate the operative results in cases in which treatment is delayed.

3. Campbell, W. C.: Fractures of the Humerus, Am. J. Surg. **38**:149 (June) 1924.

4. Cubbins, W. R., and Scuderi, C. S.: Fractures of the Humerus, J. A. M. A. **100**:1576 (May 20) 1933.

5. Colp, R., and Findlay, R. T.: Fractures of the Humerus, S. Clin. North America **8**:461 (April) 1928.

ONLAY BONE GRAFT FOR UNUNITED FRACTURES

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After using methods commonly employed for nonunion, with varying degrees of success, and after observing the method of Henderson, approximately twenty years ago I began to use the massive onlay graft. It was apparent that two factors are necessary to obtain a high percentage of excellent results in cases of nonunion: (1) absolute fixation and (2) promotion of osteogenesis (callus formation). In 1932 I presented in the ARCHIVES OF SURGERY an analysis of 125 operations. Since that time 136 additional operations have been performed, and a supplementary report is appropriate.

There is no arbitrary time for consolidation of a fracture; much depends on the degree of injury to the extremity, the soft structures involved and the efficiency of treatment. Often when union has not occurred after the lapse of sufficient time, more efficient fixation, with or without functional use of the part, may induce solidification. An ununited fracture is one in which there has been sufficient organic change to render osseous union either impossible or exceedingly improbable. No arbitrary statement can be made as to the time at which a fracture may be designated as permanently ununited, although if there has been no progress toward union at the end of six months one is justified in making the diagnosis of nonunion. There are undoubtedly instances, however, in which union has occurred after a much longer period, and not infrequently nonunion may be apparent at an earlier time. In any discussion of this subject, distinction must be made between delayed union and nonunion. In many instances this is not done; therefore, many of the data are unreliable.

In the treatment of nonunion certain inefficient methods are commonly employed and may be enumerated as follows: (1) denuding of osseous surfaces and maintaining approximation with absorbable and nonabsorbable suture (catgut, kangaroo tendon and wire); (2) application of steel and beef bone plates or pegs; (3) plastic "step-up" or dovetailed wedging of the fragments; (4) drilling of fragments, and (5) application of various types of inefficient bone grafts, such as chip grafts, Delangeniere grafts and intermedullary grafts. Such operations are performed in a high percentage of cases of ununited fracture. Union is induced in some instances by such measures, but the question

is not what nature will occasionally accomplish but by what means osseous fusion can be secured in the highest percentage of cases. With merely delayed union, consolidation can often be more rapidly induced by simple drilling of the fragments or other methods of stimulation of callus; for true nonunion, however, such measures should be discarded, as the percentage of failures is entirely too high.

For 213 patients I have employed the massive onlay bone graft on 261 bones with nonunion. The mechanical principles of this method are similar to those of a procedure employed by Henderson and were originally devised after observation of it. They differ, however, in the following respects: 1. A plain, flat surface is made for the reception of the graft, with as little removal of bone from the fragments as possible. 2. Cancellous bone is employed to promote osteogenesis as an intermedullary graft and is generously packed around the site of the fracture. 3. The endosteum is removed from the graft, the cortical portion only being utilized for fixation as well as for osteogenic purposes. 4. The graft is fixed with autogenous bone pegs instead of beef bone screws.

The details of the procedure are as follows: An ample incision is made over the point of fracture, with sharp and blunt dissection between the muscular and fascial planes to the site of the fracture, which is exposed. All intervening scar tissue is excised (fig. 1). An incision is made through the periosteum of each fragment for several inches, depending on the length and anatomic location. The periosteum is stripped from ½ to ¾ inch (1.3 to 1.9 cm.) from the circumference, the soft parts from which circulation is derived being left attached as much as possible. If there is malposition the fragments are rotated until the normal relation has been restored. If there is perfect apposition the ends of the fragments need not be disturbed, but this is comparatively rare. The fragments are pared with a chisel or a motor saw, and each medulla is reamed out (fig. 2) until normal marrow tissue is removed. With a chisel, "shavings" are removed from the circumference until there is a continuous flat surface for 3 or 4 inches (7.5 to 10 cm.), when possible, on each fragment. A broad, flat, massive graft is taken from the tibia. It should be of sufficient dimensions to assure firm fixation. With a motor saw the graft is split longitudinally through the edge or small diameter into two parts, a strong outer plate, consisting of dense bone or cortex, and an inner layer, the endosteum. A strip of endosteum is placed within the medulla, bridging the site of the fracture as reduction is made, normal marrow tissue rich in osteogenetic potentiality being thus restored. From the outer plate, or as a separate graft, a strip of dense bone (fig. 3) is taken, from which are made six or eight autogenous bone nails of appropriate size. This is accomplished
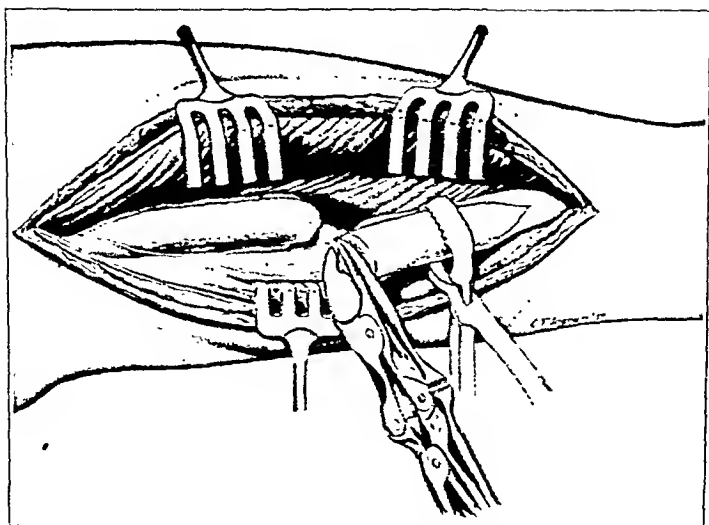
Fig. 1.—Removal of intervening fibrous tissue and freshening of the ends of the bones. The bone is stripped of as little periosteum as possible.
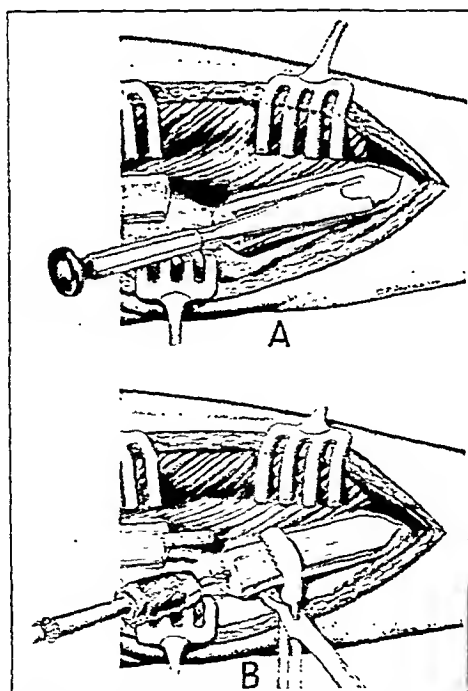
Fig. 2.—*A*, removal of "shavings" from the circumference until there is a continuous flat surface for three to four inches on each fragment. *B*, reaming out of each medulla. A strip of endosteum is placed within the medulla as the fracture is reduced.

by the aid of a rotary file (attached to the motor saw) and a metal gage to measure dimensions. The strong outer plate is held to the flat surface of the bone, passing across the site of fracture. Three or four drill holes are made through the graft and through each fragment, into which the autogenous bone nails are driven. Care should be taken not to place the autogenous pegs close to the site of fracture. The remainder of the endosteum is broken into small particles and placed with the "shavings" about the site of fracture.
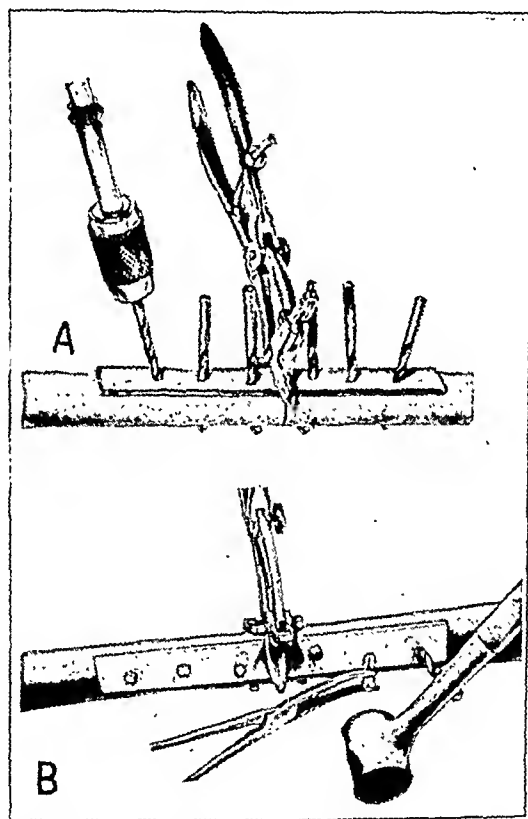
Fig. 3.—*A*, graft consisting of dense bone or cortex with drills in place. *B*, autogenous bone nails of appropriate size inserted into drill holes.

Spongy bone from the upper end of the tibia is always available and can be obtained by a sharp bone curet (fig. 4). About six pieces are removed in this manner and applied around the area of fracture. A graft of spongy bone is more proliferative than any other type of graft, being successful in 100 per cent of cases in an operation which I have devised for a type of paralytic drop foot. By this method solid fixation is attained, so that when the operation is complete no motion is apparent. Transplantation of endosteum to the medulla and cavernous bone about the fracture is an excellent method of promoting osteogenesis.

After-treatment consists in complete fixation by a plaster of paris cast or an efficient splint, which remains for a period of eight weeks. When this is removed, a convalescent splint is applied, usually in the form of a leather corset to reproduce the cast. Joints are usually incorporated, so that active and passive motion may be carried out as soon as is feasible. The brace is used until there is no doubt as to complete consolidation. The period is usually from two to four months, depending on the local condition in the case in question. Active motion may be instituted at the end of two to three months. One patient for whom this procedure was employed in both bones of the forearm left the hospital without permission at the end of twenty-four hours after operation. After a few weeks he removed the cast but obtained solid union
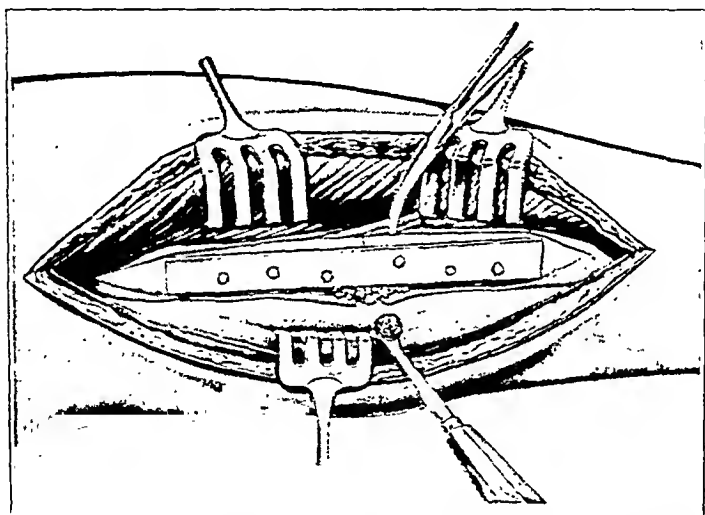
Fig. 4.—Cancellous bone from the upper end of the tibia, placed adjacent to the fracture site.

and excellent function. However, the process of bone repair, which is decreased in all fractures with nonunion, must be carefully guarded until complete consolidation occurs. Also, fracture of a bone graft with relapse to the former state of nonunion is not infrequent after the use of inefficient methods, especially the intermedullary graft. In 1 case in which I employed the intermedullary graft over twenty years ago for an ununited fracture of the lower end of the ulna, there was apparent union, but after six months there was refracture from a slight blow, and a return to the former status of nonunion occurred. In a case of ununited fracture of the humerus recently observed, there was a history of solid union after a large intermedullary graft, with refracture six months after operation, induced during swimming.

Another important factor is that the graft must not be applied under tension or there will be gradual dissolution at the point of tension. This has been observed in bone grafts to the spine which were employed under tension to conform to kyphosis or when kyphosis has occurred after the graft was employed.

Fig. 5.—Nonunion of the humerus.

The graft under discussion is a massive onlay graft and must be efficiently applied as described; otherwise the procedure is a caricature of the correct operation. Frequently, illustrations in the literature have demonstrated that this method has been inadequately employed. Excellent results obtained by the method have been reported by Dr. Barnett Owen of Louisville, Ky., Dr. Kelly West of Oklahoma City, Dr. J. S. Norman of Pueblo, Colo., and (in personal communications) Dr. John Wilson of Los Angeles and others.

The importance of complete internal fixation as described has been demonstrated by others in reports of excellent end results. Albee has employed the inlay method and has claimed that he can secure complete
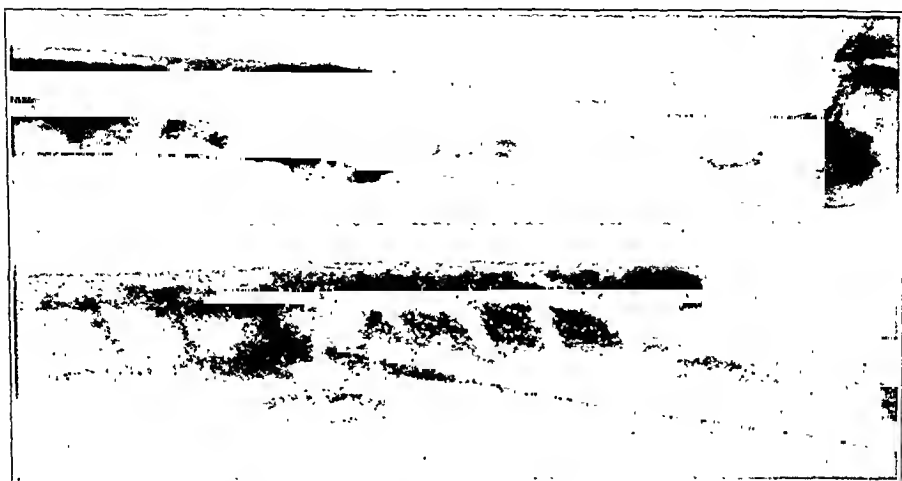
Fig. 6.—Fracture shown in figure 5, three months after onlay bone graft.
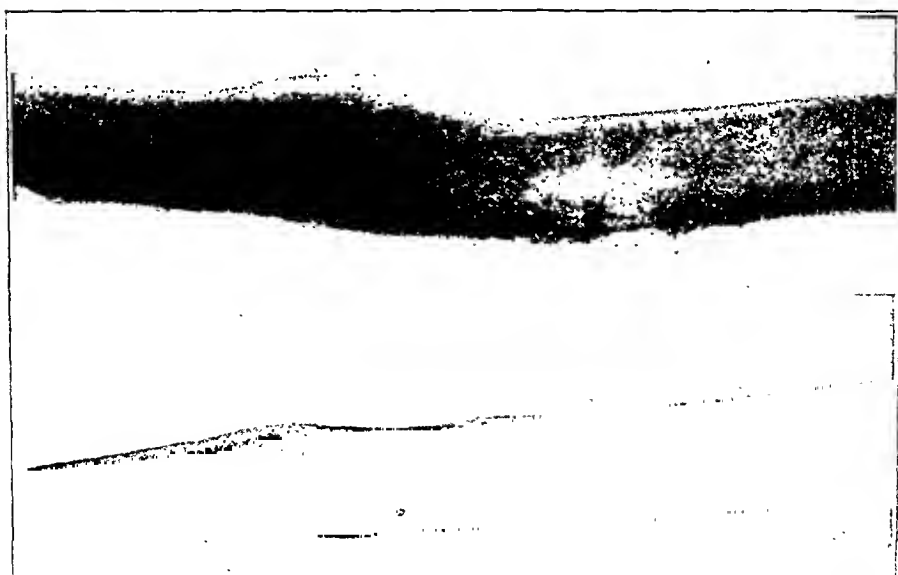
Fig. 7.—Fracture shown in figure 5, six years after onlay bone graft. Note increased dimension and strength of bone as obtained by the onlay method.

fixation, but I was unable to secure this after many attempts. Gill stated that he removes a massive graft of one-half the circumference of the bone and employs it as a graft across the line of fracture, which

is solidly fixed with steel screws. O'Neill Sherman stated that he employs a massive graft from the tibia, which is fixed within the medullary cavity across the line of fracture by steel screws. These methods have the disadvantage of removal of a large portion of the circumference of
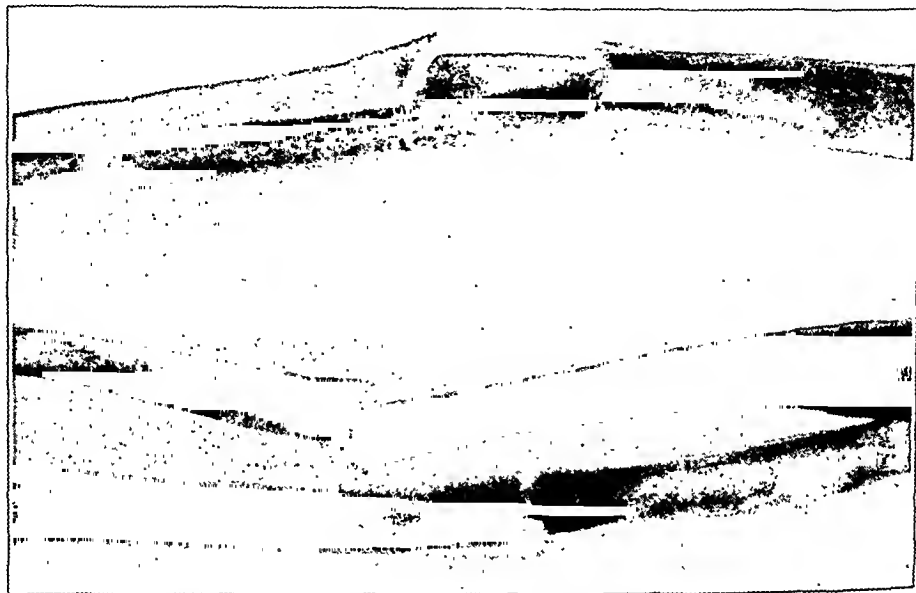
Fig. 8.—Nonunion of both bones of the forearm.
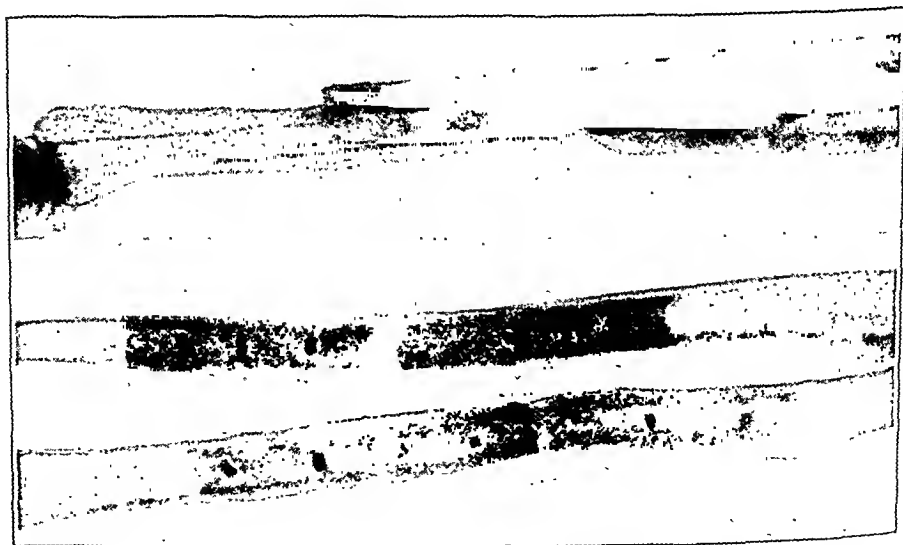
Fig. 9.—Fracture shown in figure 8, five months after onlay bone graft.

the fragments from which union is finally to be secured. In case of infection with extrusion of the graft, there is loss in the circumference and at times in continuity, and the chance of success by subsequent procedures is decreased.

Recently, Bennett has reported success in 10 cases of fracture of the humerus. treated by a method which consists of making long oblique fragments, after which beef bone nails are employed to transfix the fragments. The disadvantage of this method is that the arm is definitely shortened. I reported the same procedure for oblique ununited fractures, with the exception that autogenous nails were employed. However, nonunion of oblique fractures is exceedingly rare.
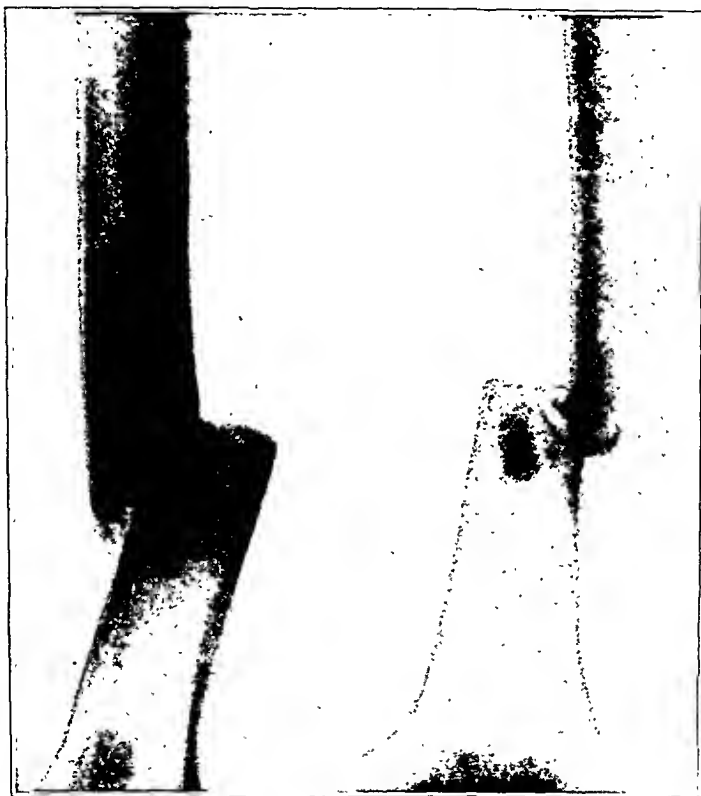
Fig. 10.—Nonunion of the femur.

Harkins and Phemister have advanced as criticisms of the massive onlay graft that the procedure carries some risk of infection and in the case of long bones, particularly the femur, of hemorrhage and shock, and that resection of the fragment ends results in shortening of the bone to an objectionable extent. These have not proved to be serious objections in my experience. In this series there were 31 cases of infection. In 29 the infection occurred in a compound fracture; in all but 2 cases it could be attributed to the relighting of a previous pyogenic infection. No undue shock or excessive shortening has occurred. With these objec-

tions in mind, Harkins and Phemister advised laying onlay grafts across the fracture line without fixation and without disturbing the site of fracture to any appreciable degree. This method was devised only for cases of nonunion in which displacement is not marked.

ANALYSIS OF CASES •

In 1932 an analysis of the end results in 104 cases was made, and the same plan will be employed on this occasion for 261 bones of 213 patients.
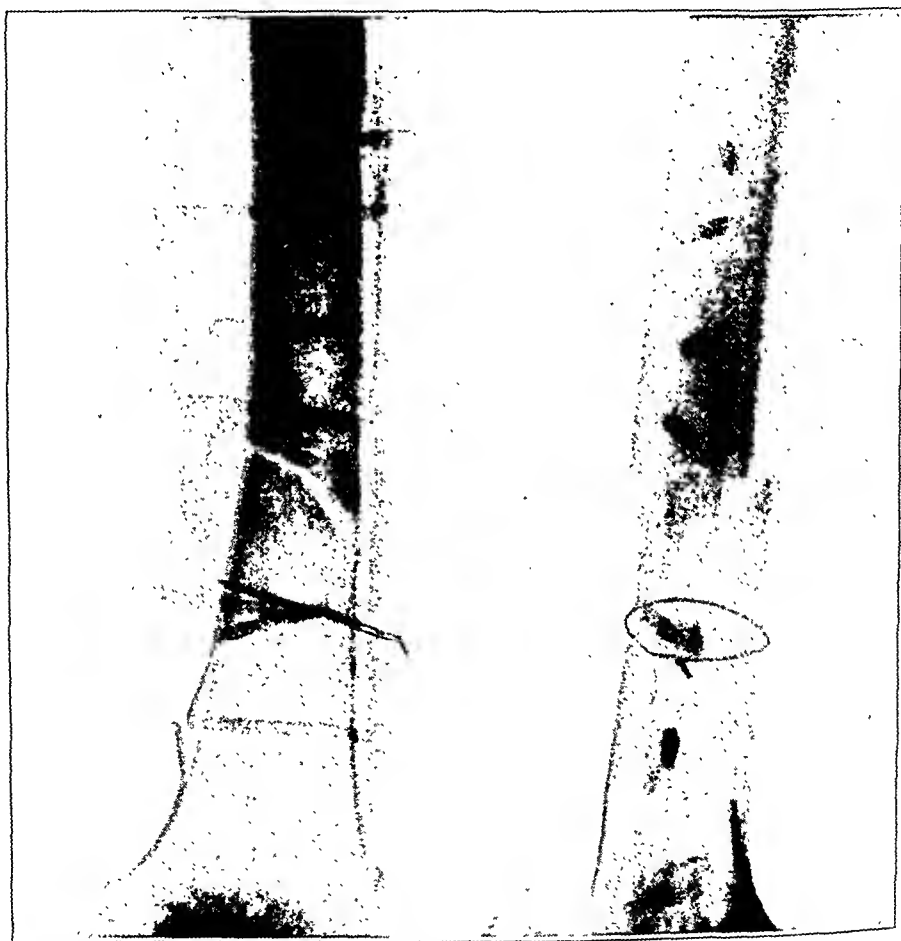
Fig. 11.—Fracture shown in figure 10, two months after onlay bone graft.

When bone grafts were employed as entirely separate surgical procedures for nonunion of two bones of the same patient, for example, the radius and the ulna, the procedures were listed as two operations, as each was a separate surgical equation. Similarly, failures have been counted in the same manner. When a bone was regrafted, as occurred in 5 instances in this series, two operations were reported, one as a failure and one as a success. Hence the apparent discrepancy between the number of patients and the number of operations.

END RESULTS OF TWO HUNDRED AND SIXTY-ONE OPERATIONS

Number of operations	261
Number of patients	213
Males	180
Females	33
Ages (5 to 62)	
Patients under 20 years of age	20
Patients above 50 years of age	15
Solid union	15
Length of time since fracture	4 mo. to 8 yr.
Approximate average length of time since fracture	14 mo.
Cases in which there had been 1 to 4 previous operations	58
Gunshot or compound fractures	55
Failures in cases with history of compound fracture	7
Time elapsed too short to permit determination of union or result unknown	10
Failures	16
Regrafting performed for failures	5
Solid union	5
Solid union, total	235
Percentage of instances of solid union induced in 251 operations	93.6

POSTOPERATIVE INFECTIONS

Number of cases	31
Osseous union induced	24
Sequestration of part of or entire graft	24
Failure of union after sequestration	7
Cases with history of previous pyogenic infection	24
Compound fractures without infection	5
Simple fractures	2

RESULTS OF ONLAY GRAFTS IN DIFFERENT REGIONS

Tibia

Number of operations	59
Solid union	54
Failures	5
Percentage of instances of solid union	91.5

Humerus

Number of operations	60
Solid union	57
Failures	3
Percentage of instances of solid union	95

Femur

Number of operations	36
Solid union	33
Failures	3
Percentage of instances of solid union	91.6

Radius

Number of operations	23
Solid union	22
Failures	1
Percentage of instances of solid union	95

Ulna

Number of operations	15
Solid union	14
Failures	1
Percentage of instances of solid union	93

Radius and Ulna

Number of operations	58
Solid union	55
Failures—(radius 1, ulna 2)	3
Percentage of instances of solid union	94

The chances of success with bone grafts are thought to be less when patients are of advanced age, but it is interesting to note that in this series in the 15 patients above the age of 50 the grafts were 100 per cent successful. In the oldest patient, aged 62 (a patient not included in this report was 72), nonunion had existed for seven months. Not only did union occur uneventfully after operation, but the patient was able to return to his former occupation, as a laborer on the railroad. Of the 251 ununited fractures, 55, or approximately 22 per cent, were
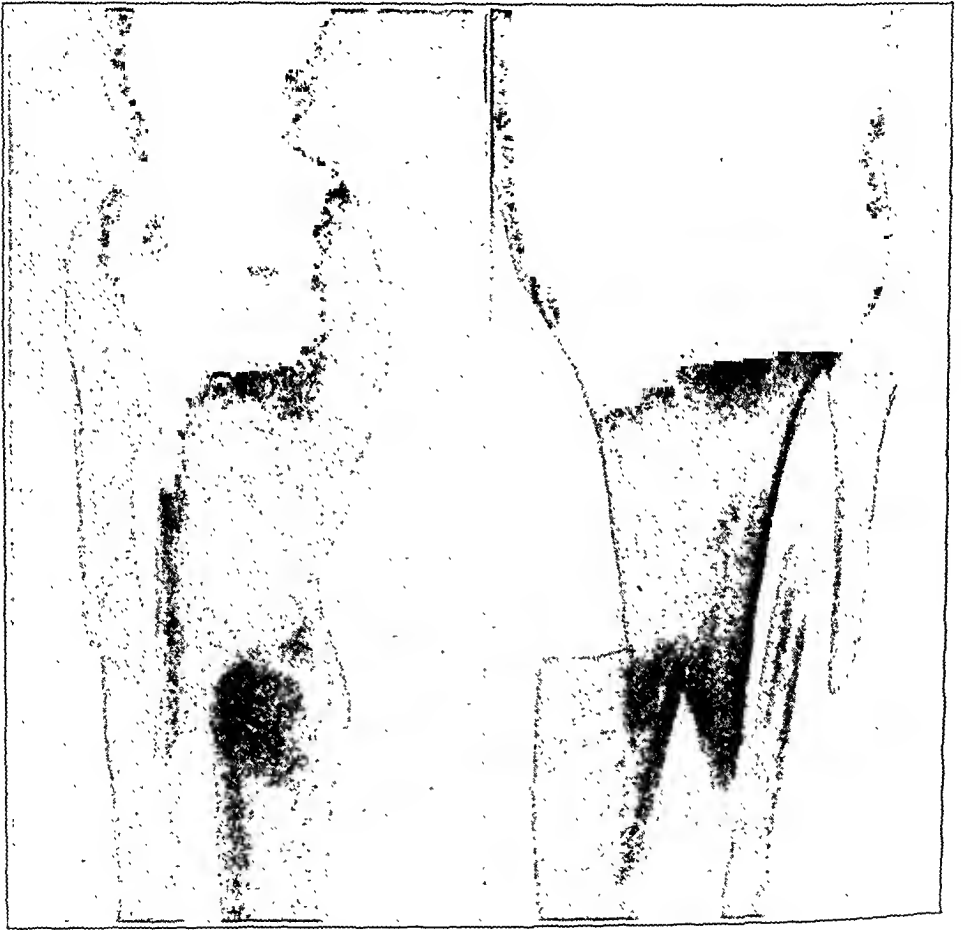
Fig. 12.—Nonunion of the tibia.

compound or gunshot fractures, which is surely suggestive, if not absolutely conclusive, that compound fractures have a definite causative relation to ununited fractures. Of the 55 ununited fractures which had been originally open or compound, there were 7 in which union failed to be induced. Only those in which there was frank pus with definite constitutional symptoms of pyogenic infection are considered as presenting infection. Union was induced regardless of an intense infection in 24 of the 31 cases in which infection was present. In 7 the graft remained intact, while in 24 there was sequestration of a part of the transplant.

In 17 of these 24 cases, regardless of sequestration, the graft functioned for sufficient time to induce union.

In this series there were 16 cases in which the onlay method failed to produce union. In 2 cases of nonunion of both bones of the forearm, fusion was induced in the ulna but not in the radius; function, however, for each patient was so satisfactory as compared with the former status that further operative measures were declined. The causes of the 16 failures may be analyzed as follows: Eight were due to technical errors
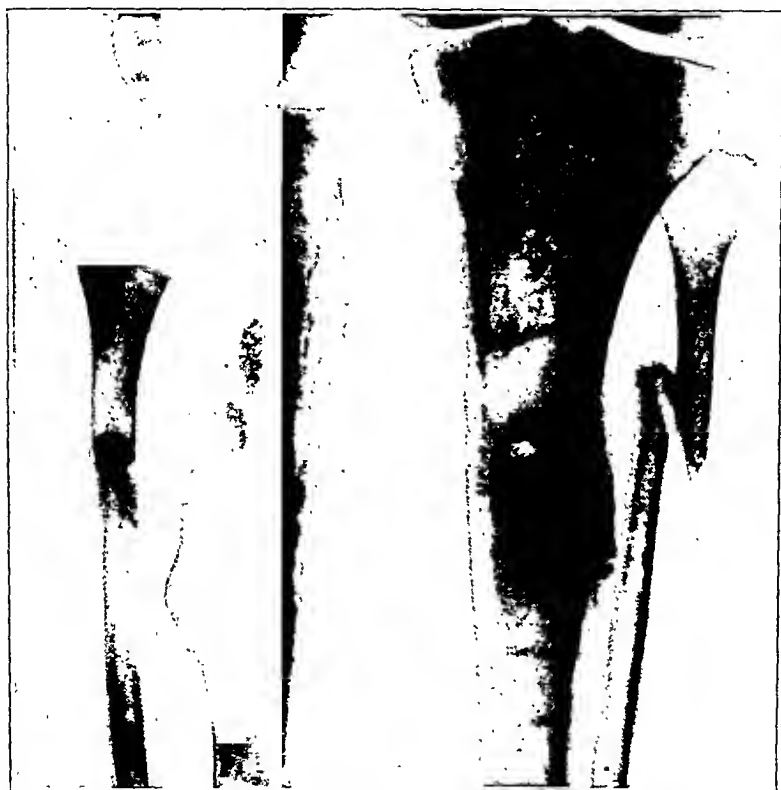
Fig. 13.—Fracture shown in figure 12, six months after onlay bone graft.

(fracture of the graft, poor approximation of the fragments or separation of the graft from the fragment); 7 were due to infection and sequestration; 1 was due to lack of osteogenesis, possibly constitutional. In 5 of these cases regrafting was successfully done.

A careful review has been made of serial roentgenograms at intervals of approximately thirty to sixty days for the first six months, and in many cases for two years. When there was satisfactory application, as denoted by close contact of the graft fragments, there was no change in density or structure of the graft, which apparently fused to the host,

increased in size and became gradually assimilated. The bone nails gradually disappeared, but there was usually permanent evidence of the graft, as denoted by an increase in diameter of the shaft. In cases with extensive atrophy of bone, union was secured, though delayed, evidently because of the fact that fixation was not as firm. In many, proliferation of the transplanted endosteum and spongy bone about the site of fracture was apparent by the end of eight weeks. In a small number, satisfactory approximation was not maintained between the graft and the shaft of the bone over a portion of the graft. In these there was definite evidence of absorption and distintegration, as denoted by enlargement of the drill holes and punched-out areas in the graft where it was not in contact. At those parts in which there was approximation, however, the integrity of the graft was not involved, and fusion continued. This did not apparently affect the end result, as fixation was secure except that it was thought necessary to continue the use of external apparatus for a longer period.

When there was a primary infection or an old infection was relighted by operation, gradual disintegration with absorption of a portion of the graft or all of it was noted in 24 cases; often there was also evidence of new bone formation, especially along the line of the fracture, where endosteum and spongy bone had been transplanted. Fixation, however, was usually maintained for a sufficient time to permit osseous union of the fracture, so that the function of the graft was accomplished. The graft, or a portion thereof, in such cases acted partly as a foreign body, but it is believed that an autogenous graft, even though infected, is better tolerated by the tissues than is foreign material.

In a small number of cases the wound failed to heal by primary intention, as evidenced by persistent drainage for several weeks. Whether the condition in these cases should be classed as mild infection or as caused by undue hemorrhage from the bone with persistent seepage of serum is a moot question. At any rate, such a condition is often observed after an extensive operation on bone. In this type of case the roentgenogram demonstrated disintegration of the graft, similar to the changes previously described as occurring in cases in which mechanical approximation was not obtained. Also, such changes were occasionally seen when there was primary healing of the wound, but in by far the greater number of cases the graft apparently assumed an active part in physiologic bone construction.

Union of ununited fractures is secured by two different processes: functional adaptation of the graft, as may be denoted by hypertrophy, and union of the fragments themselves. Fractures of the graft have occurred when protection was not sufficient or when there was undue tension on the graft or drill holes too near the fracture site, owing to

an error in surgical technic, but always within a period of three months. In those instances in which osteogenesis is exceedingly deficient in the fragments, union must be accomplished largely by graft alone, with gradual fusion of the fragments by a process of functional adaptation along the lines of stress. In such cases protection must be continued for a longer period. In most instances union is induced between the fragments, but it is much slower than in fresh fractures; therefore, it required the services of a graft which in addition to promoting osteogenesis is able to hold the fragments absolutely fixed.

CONCLUSIONS

1. Union is accomplished in a shorter time by the massive onlay transplant than by other operations generally used, as evidenced by the fact that no motion can be detected from the time the operation is completed.

2. Earlier movement is permitted in adjacent joints. and thus function is conserved.

3. The onlay graft actually increases the dimension and strength of the bone; the circumference is maintained intact. Practically no bone is excised, but new bone is added.

4. Of 31 patients with postoperative infection. 24. or 77.4 per cent, showed solid union.

5. Solid union was secured by means of the onlay graft in 235, or 93.6 per cent, of 251 cases.

6. The criticism has been made that the operation is too technical or difficult, requiring a well trained team of at least two experts and three assistants, but the means are surely justified if the percentage of good results can be materially increased thereby.

ORAL ADMINISTRATION OF METHYL-CHOLANTHRENE TO MICE

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Experiments to produce cutaneous carcinoma by application of tar and, more recently, of the several synthesized carcinogenic compounds and to produce sarcoma by subcutaneous or intramuscular injection of these substances have been repeatedly performed on mice, rats, rabbits and guinea pigs. A significant percentage of pulmonary tumors has been observed as a result of cutaneous application of the compounds. However, relatively fewer observations have been published on the production of "internal cancers" by causing the animals to ingest the various carcinogenic agents in one form or another.

By repeated tarring of the mouths of 50 rats Bonne[1] produced benign papillomas in the skin of the face about the mouth and also squamous cell carcinomas in the buccal cavity, the esophagus and the cardiac end of the stomach. Voronoff and Alexandrescu[2] administered a mixture of tar, hydrous wool fat, aniline oil and toluylenediamine by mouth to 10 rats and observed 1 papilloma of the tongue and 1 carcinoma of the stomach. A number of negative reports from oral administration of tar have been made by other observers. Reinhard and Candee[3] did not observe benign or malignant tumor formation in mice fed dibenzanthracene mixed with butter, during a period of seven months. Ilfeld[4] inserted dibenzanthracene pellets into the gastric wall of a dog and pellets of benzpyrene under the gastric mucosa of 6 ferrets, with negative results after one year. Oberling[5] also obtained negative results after feeding benzpyrene to rats and mice for periods of six to ten months. On the other hand, Waterman[6] observed carcinomas of the

1. Bonne, C.: Ztschr. f. Krebsforsch. 25:1, 1927.
2. Voronoff, S., and Alexandrescu, G.: Néoplasmes 8:129, 1929.
3. Reinhard, M. C., and Candee, C. F.: Am. J. Cancer 26:552, 1936.
4. Ilfeld, F. W.: Am. J. Cancer 26:743, 1936.
5. Oberling, C., and others: Bull. Asoc. franç. p. l'étude du cancer 25:156, 1936.
6. Waterman, N.: Acta brev. Neerland. 1:18, 1937; abstracted, Am. J. Cancer 30:379, 1937.

stomach, 4 with metastases, in 5 mice which had been fed several milligrams per day of benzpyrene in lard for periods varying from one hundred and twelve to three hundred and thirty-six days.

We obtained negative results from feeding dibenzanthracene in lard to white mice three times a week for six months. (These mice were from the same colony as those to be described.) Recently Rowntree and his associates [7] observed multiple intra-abdominal spindle cell sarcomas in rats fed crude wheat germ oil. No epithelial neoplasms were reported. Yoshida [8] induced carcinoma of the liver in rats by feeding 2-amino—5 azotoluene. Otsaka [9] observed papillomatosis in the fundi of the stomachs of mice fed diazoaminobenzene.

TABLE 1.—*Results of Experiment 1*

Mouse	Period of Methylcholanthrene Administration Days	Necropsy
BW 1	164	Marked emaciation; small, rounded pedunculated papilloma approximately 1.5 mm. in diameter in fundus of stomach; microscopic section not obtained
BW 2	168	Large fusiform mass about right mandible, with extension into neck; flat grayish ulcer along right gum margin; microscopic examination showed squamous cell carcinoma arising over right gum with secondary invasion of mandible and direct extension into neck
BW 3	169	Squamous cell carcinoma 0.5 cm. in diameter arising in skin of the chin and not connected with the mucosa of the lower lip; large ulcerating carcinoma of left anterior breast
BW 4	1C9	Several small benign epithelial papillomas on chin; large ulcerating carcinoma of second left breast
BW 5	178	Benign papilloma of skin of right mandible; ulcerating carcinomas of the left anterior 2d and 3d breasts with pulmonary metastasis
BW 6	175	Benign squamous cell papilloma in upper portion of stomach where mucosa is squamous epithelium; carcinoma of 2d left anterior breast; squamous cell carcinoma of skin of right side of neck; nonmalignant chronic ulcer on right side of nose
BW 7	186	No tumor
BW 8	186	Squamous cell carcinoma 0.6 cm. in diameter on right side of chin; nonneoplastic ulcer just to the left of this

Because methylcholanthrene, one of the most potent carcinogens, is chemically related to bile acids [10] and because bile or its decomposition products normally bathe a large portion of the alimentary canal, the following feeding experiments with this substance were performed.

EXPERIMENT 1.—Fifteen white mice of unknown genetic history, obtained from a commercial dealer's inbred colony and at least 6 months old, were given 2 minims (0.12 cc.) of a 1 per cent solution of methylcholanthrene in olive oil three times a week. To prepare this solution it was necessary to heat the olive oil prior to admixture with the substance; as the olive oil cooled the methylcholanthrene did not crystallize out of solution. The mice were held firmly back downward while the material was forced into the mouth by means of a glass dropper. Some of it was swallowed

7. Rowntree, L. G., and others: Am. J. Cancer **30**:359, 1937.

8. Yoshida, T.: Tr. Jap. Path. Soc. **23**:636, 1933.

9. Otsaka, S.: Gann **29**:209, 1935.

10. Fieser, L. F.: The Chemistry of Natural Products Related to Phenanthrene, New York, Reinhold Publishing Corporation, 1936.

immediately; some remained in the mouth for a short period, and some spread over the face, the neck and the anterior portion of the thorax. Eight mice survived for the duration of the experiment, approximately six months. In those dying after shorter intervals, no lesions were observed at necropsy.

The animals were killed as they became weak and emaciated and apparently would die in a few days. The results are recorded in table 1.

Observations on large numbers of mice obtained in the course of other experiments and procured from the same dealer's stock showed that in
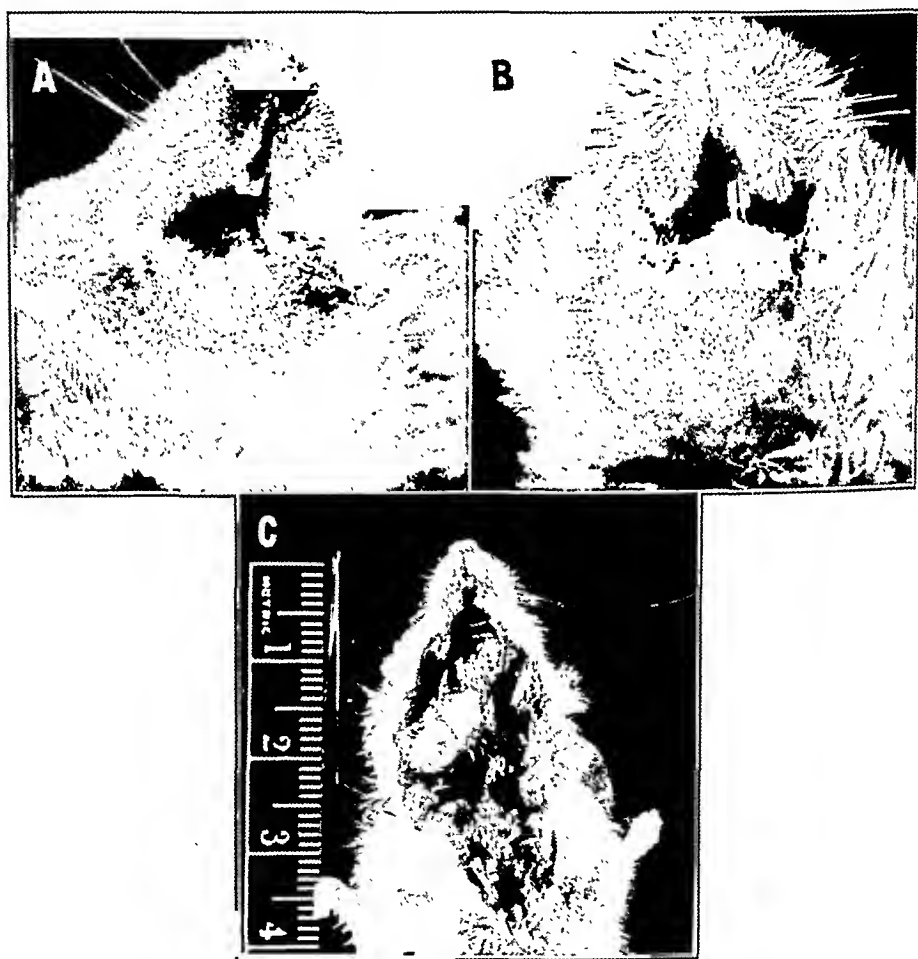
Fig. 1.—A (mouse BP1), squamous cell carcinoma of the left angle of the mouth, involving the inner aspect of the left cheek of a mouse fed methylcholanthrene over a period of sixty-seven days. The photograph was taken twenty-two days after the first appearance of the lesion. B, large swelling over the right mandible and the floor of the mouth, caused by a squamous cell carcinoma arising in the mucosa over the right mandible and spreading over the floor of the buccal cavity. The photograph was taken one hundred and sixty-eight days after feeding with methylcholanthrene was started. (Mouse BW2.) C, large squamous cell carcinoma arising in the right wall of the hypopharynx, extending outward to the base of the right ear. The photograph was taken one hundred and forty days after the beginning of the experiment. (Mouse BP2.)

Fig. 2 (mouse BW2).—Photomicrograph of a squamous cell carcinoma of the mucosa over the right mandible, showing invasion of the latter and infiltration about the tooth (*T*). *M*, normal buccal mucosa. *C*, infiltrating carcinoma.

Fig. 3.—Stomach of mouse killed one hundred and sixty-four days after the beginning of the experiment. *C*, forestomach, lined by stratified squamous epithelium. *S*, midportion and pyloric portion, lined by typical gastric mucosa. *P*, benign squamous cell papilloma.

15 to 20 per cent of the females of this strain spontaneous mammary tumors developed. Of the 7 animals for which positive results were obtained in the aforementioned series, 4 had carcinoma of the breast after at least one hundred days from the beginning of the experiment. While it is probable that these tumors were not related to the applications of methylcholanthrene, it must be pointed out that all of the mammary tumors arose well forward on the thorax, an area over which the oil solution spread at each intra-oral application.

Fig. 4 (mouse BW6).—Photomicrograph of a benign squamous cell papilloma in the cardiac portion of the stomach.

EXPERIMENT 2.—Methylcholanthrene was dissolved in lard to make a 1 per cent solution by weight. By means of a small glass syringe and a filed-off 18 gage needle, 2 minims (0.12 cc.) of the mixture was injected into the mouths of the animals every other day for four months. The administrations were then reduced to twice a week. The material was injected slowly in order that the animals might immediately swallow as much as possible. In contrast to the first experiment, a relatively small amount of the substance escaped over the face and anterior part of the body. Of a total of 33 animals, positive results were observed for only

2. Many of the animals became toxic in the earlier weeks of administration and died. The longest survivor lived one hundred and sixty days. The positive results are summarized in table 2. Complete autopsies were done on all animals. There were no papillomatous or other lesions in the stomachs or intestinal tracts in any of the animals examined in the second group.

TABLE 2.—*Results of Experiment 2*

Mouse	Period of Methylcholanthrene Administration Days	Necropsy
BP 1	67	Small rounded carcinoma at left angle of mouth, increasing in size to 89th day, when it measured 8 mm. in diameter; animal died spontaneously; lesion involved the mucosa of the cheek as well as the skin on the outer aspect; microscopic examination showed squamous cell carcinoma
BP 25	140	Animal died spontaneously; on the right side of the hypopharynx and extending through to the base of the right ear there was an oval firm whitish mass 15 by 8 mm.; microscopic examination showed squamous cell carcinoma

COMMENT

From these experiments it would appear that although methylcholanthrene, as has been stated, is chemically related to bile acids, it does not exhibit a marked degree of potency on oral administration as regards induction of neoplasms even in the upper regions of the alimentary canal, where the lining is stratified squamous epithelium. Failure to produce lesions in the glandular epithelium of the lower part of the stomach and in the intestines might, in addition to a high degree of resistance on the part of such epithelium, be explained by certain mechanical factors. Whereas in cutaneous application and subcutaneous injection of the carcinogens certain prolonged contacts of cells with the substances obtain, in the alimentary canal there is a constant "wash" of materials over the surfaces. Furthermore, these surfaces are covered by a layer of mucus.

SUMMARY

Because of the chemical relationship of methylcholanthrene, one of the most potent carcinogens, to bile acids, which normally bathe a large portion of the gastrointestinal tract, feeding experiments with this substance were carried out on mice.

Of 48 mice observed for periods ranging up to one hundred and eighty-six days, 2 presented benign squamous epithelial papilloma of the fundus of the stomach. One of these also presented a carcinoma of the outer aspect of the right cheek. 1 a carcinoma of the buccal mucosa over the mandible with invasion of the latter. 1 a hypopharyngeal carcinoma. 1 a carcinoma of the angle of the mouth. involving the mucosa and the contiguous skin of the cheek. 1 a squamous cell carcinoma of the skin on the right side of the chin. 1 a benign papilloma of the skin over the right mandible and 1 several small papillomas scattered over the chin.

AVULSION FRACTURE OF THE GREAT TROCHANTER

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Interest in the present study of isolated fracture of the great trochanter was stimulated by a necessity which recently arose for answering questions having medicolegal significance. The need for such a study was appreciated the more when it was realized that, instead of being casual and commonplace, this type of fracture is extremely interesting and unusual.[1] In spite of carrying on a moderately active hospital and private practice involving the treatment of many industrial accidents, I have personally observed only 3 cases during more than fifteen years. A fairly careful search by the attending roentgenologist of the extensive dispensary and inpatient files of the roentgenologic department of the Hospital for Joint Diseases disclosed only 4 additional cases classified under the diagnosis of fracture of the great trochanter. Final recourse to a number of standard textbooks dealing with the subject of fractures[2] was but slightly more gratifying, if at all. One author dismissed the subject without mention. Another described only the epiphysial separation occurring in patients under the age of 18. Others gave descriptions, which, though more extensive and extremely helpful, still did not clearly define the clinical picture in terms which

1. (a) Eboil, J.: Ann. brasil. de med., Rio de Janeiro **29**:76, 1877. (b) Feinen, J.: Deutsche Ztschr. f. Chir. **99**:444, 1909. (c) Krüger: ibid. **83**:464, 1906. (d) Neugebauer, G.: Med. Klin. **17**:1358, 1921. (e) Stein: Deutsche med. Wchnschr. **32**:818, 1906.

2. (a) Key, J. A., and Conwell, H. E.: The Management of Fractures, Dislocations and Sprains, St. Louis, C. V. Mosby Company, 1934, p. 780. (b) Magnuson, P. B.: Fractures, Philadelphia, J. B. Lippincott Company, 1933. (c) Scudder, C. L.: The Treatment of Fractures, with Notes upon a Few Common Dislocations, ed. 10, Philadelphia, W. B. Saunders Company, 1926, p. 530. (d) Speed, K.: A Text-Book of Fractures and Dislocations, Philadelphia, Lea & Febiger, 1916, p. 397. (c) Stimson, L. A.: A Practical Treatise on Fractures and Dislocations, ed. 8, Philadelphia, Lea & Febiger, 1917, p. 397. (f) Wilson, P. D., and Cochrane, W. A.: Fractures and Dislocations, Philadelphia, J. B. Lippincott Company, 1925, p. 515.

fit the cases here studied. Because of this it is felt that presentation of even limited material will be condoned.

While a series of 7 cases would not seem to warrant the didactic setting up of any elaborate system of classification, it will be noted that the cases here reported cannot be discussed together unless it is clearly realized that they fall naturally into three smaller categories. On the basis of the age of the patient, fractures of the great trochanter may be divided into the epiphysial separations of adolescence and the true fractures of adulthood. The former occur in patients under the age of 18, before the closure of the epiphysial line, and involve the whole of the great trochanter. The latter usually do not involve the whole of the trochanter and, on the basis of the etiologic mechanism, may be subdivided into those which are caused by accidental injury and those which are due to muscular violence. In the present series 6 cases of true fracture and 1 of epiphysial separation were found.

REPORT OF CASE OF EPIPHYSIAL SEPARATION

CASE 1.—Rita B., aged 3 years, first appeared in the outpatient service in December 1930, with a flexion contracture of the elbow. There was a history of multiple articular disease following pyemia, for which the patient had been treated in another institution before her admission to the Hospital for Joint Diseases. On Oct. 5, 1935, it is recorded that the patient, then aged 8 years, had fallen while skating and had suffered "complete oblique fracture at the junction of the middle and distal thirds of the shaft of the left tibia, with good alinement of the fragments." A plaster bandage was applied and was left on until Dec. 14, 1935. In February 1936 it was noted that "the child walks with a slight limp on the left side, holding the left foot everted. Examination shows apparently good healing of the line of fracture—no shortening and no tenderness. The foot is somewhat swollen." In October 1936 it was first noted that "the patient complains of pain in both lower limbs, mainly the left one. Examination of the foot gave results essentially negative." A diagnosis of epiphysiolysis was made, and a roentgenogram of the left hip was requested. Though the symptoms did not seem to point to involvement of the right hip, roentgenograms were made of both hips for comparison. This film (fig. 1) was reported by Dr. M. M. Pomeranz to show "a fragmentation of the right greater trochanter, with separation of two small fragments of bone. There is a slight hiatus between the greater trochanter and the shaft of the femur at the epiphysial line. No such hiatus exists in the identical area on the opposite side. Extending from the base of the epiphysis downward in the soft tissues, external to the femoral shaft, for a distance of 3 inches (7.6 cm.), linear calcification is present. The diagnosis is fracture of the epiphysis of the greater trochanter with an ossifying process in the soft tissues of the thigh below."

ETIOLOGY

Apart from the question of diagnosis, the main interest in fracture of the trochanter lies in the discussion of the mechanism of its production. While it is true that in the preceding case there was antecedent trauma, the relationship of the direct injury in the left leg to

the roentgenographic signs inadvertently found in the opposite leg may well be questioned. Moreover, the presence of an earlier infection and the possibility that an unnoticed muscular injury to the right leg may have been suffered at the time of the original accident serve to stimulate a wide difference of opinion as to the ultimate cause, though the fracture is probably to be grouped among the epiphysial separations.

Fig. 1 (case 1).—The calcific shadow is disposed over the whole length of the trochanter and extends into the soft tissues. There is a slight increase in the width of the epiphysial line as compared with that on the opposite side. The fragmented shadow is reminiscent of the picture occasionally seen in periosteal ossification or in peritrochanteric bursitis.

With epiphysial separations occurring as they do during the period of greatest growth, it would seem reasonable to attribute them to trauma or to the avulsing action of the muscles which are inserted into the trochanter. On this question, however, there appears to be

considerable difference of opinion in the literature. Poland [3] stated, ". . . that the injury is almost always the result of direct violence, such as a fall on the hip, or a severe blow on the trochanter." Though he noted the frequency with which infection was associated with epiphysial separation, he did not particularly stress the relationship. Similarly, he mentioned several cases in which muscular pull might have been considered the causative factor, but he specifically deprecated the validity of the supposition as unproved by autopsy. Stimson,[2e] on the other hand, commented: "In all but one (Daniels) the separation was exactly along the epiphysial line and the fragment was not displaced; it seems highly probable that they were cases of osteomyelitis, possibly originating in trauma."

In the more recent writings on this subject,[4] the significance of infection is almost completely neglected in favor of direct blows or indirect muscular violence. Unfortunately, epiphysial separations and forms of fracture which occur in adults are grouped together in these later discussions. Though casual mention is made of the fact that fractures of the trochanter in adults may result from muscular effort, the impression is conveyed that avulsion more commonly occurs in cases of epiphysial separation of adolescence, while direct violence is the more common cause of fracture in adults. Thus Speed, in the most recent edition of his excellent textbook, stated:

> This fracture (of the great trochanter) is infrequent and is caused either by direct violence received on the trochanter, or by muscular action of the external rotators of the thigh attached to the great trochanter, accompanied by torsion of the whole limb inward. In the latter instance, the separation generally follows the old epiphyseal plane, especially when it occurs in adolescence.

With this opinion the experience gained in the present series is only partially in accord. It appears that those epiphysial separations which may be attributed to muscular action can be explained only on the assumption that the gluteal muscles, and not the external rotators, are the disrupting force. On the other hand, it appears that the external rotators result in an avulsion fracture of the tip rather than of the body of the great trochanter. Contrary to the general belief that direct external trauma is the most common cause of these fractures, the cases here recorded lead to the conviction that the larger number are caused by indirect muscular violence. Of the 6 fractures in adults only 1 (case 2) can be unequivocally attributed to a direct blow, while the other 5, due to muscular action, constitute a subgroup as characteristic of the adult as epiphysial separation is of the adolescent.

3. Poland, J.: Traumatic Separation of the Epiphyses, London, Smith, Elder & Co., 1898, p. 662.

4. (*a*) Kummer, A.: Nederl. tijdschr. v. geneesk. **78**:1324, 1934. (*b*) Key and Conwell.[2a] (*c*) Scudder.[2c] (*d*) Speed.[2d]

REPORT OF CASES OF TRUE FRACTURE IN ADULTS

The case which immediately follows, that of a fracture due to a direct blow, is presented in the barest detail and largely for contrast with the succeeding 5 cases, which illustrate the main theme of this communication—avulsion fractures of the tip of the great trochanter.

Fig. 2 (case 2).—Small chip fracture off the upper portion of the trochanter, due to a severe external blow.

CASE 2.—Robert N., a contractor aged 25, was admitted to the hospital on July 20, 1928. The patient stated that while descending from a trolley car he had been struck and thrown down by a passing automobile truck. He was taken to a municipal hospital, where it is alleged that a dislocation of the left hip was reduced. On admission to the Hospital for Joint Diseases the patient showed abrasions and contusions about the left ilium and walked with difficulty. Roentgen examination "disclosed the hip in marked abduction, with a chip off the greater trochanter at its upper and anterior margin" (fig. 2). No statement of the treatment was made. Six days after admission the patient was discharged. In

October 1930 he again visited his physician, this time with a complaint of pain, especially on change of weather. Examination at this time elicited no objective evidence of any disability attributable to the earlier injury.

CASE 3.—Bertha L., a housewife aged 70, was admitted to the hospital on Nov. 12, 1932. She had fallen on her left side and afterward had been unable to get up or to walk. She had been brought to the hospital in an ambulance.

Examination disclosed no shortening of the limb. The distance from the anterior superior spine of the ilium to the internal malleolus of the tibia measured for the

Fig. 3 (case 3).—Typical avulsion fracture of the great trochanter at its posterosuperior angle. The line of fracture is approximately at the level of the junction of the trochanter and the neck. The leg is in slight external rotation.

right leg 30⅜ inches (77.2 cm.) and for the left 30¼ inches (76.8 cm.). The left limb was held in 5 degree adduction and in 10 degree external rotation. Adduction was possible to 20 degrees and flexion to 90 degrees, with pain. A roentgenogram (fig. 3) "disclosed a complete fracture through the greater trochanter, with upward and inward displacement of the fractured fragment." Traction was applied to the limb. On Nov. 29, 1932, the patient was discharged. No subsequent data on this case could be obtained.

CASE 4.—Thomas M., aged 48, was seen in the outpatient department on March 19, 1934, with a history of having fallen and "struck the stump of his amputated left leg some twelve days before. He had pain and tenderness in the region of the trochanter." Later, "considerable local induration of the great trochanter was noted." The roentgenogram was reported by Dr. Pomeranz as showing "complete oblique fracture of the greater trochanter. The line of fracture begins at the inner aspect of the base of this prominence and extends obliquely upward and outward to the cortex ½ inch (1.3 cm.) below its upper limit. At the latter site two small spicules of bone are noted. There is no separation of the fragments." (The line of fracture was almost identical with that seen in the other similar cases; a reproduction was not prepared because the line was just barely discernible on the original roentgenographic plate.) Physical therapy was prescribed, with the understanding that if there was no improvement a plaster of paris spica was to be applied. In the absence of any contrary note in the record, the inference may be drawn that there was no need for any modification of the treatment employed. The patient later disappeared from observation.

CASE 5.—Harry La C., a janitor aged 47, fell off a ladder while at work on Sept. 10, 1934. The patient complained of moderate pain over the great trochanter and of limitation of motion in the hip. There was tenderness on pressure over the trochanter but no evidence of ecchymosis or of injury to the overlying soft tissues. Both legs were of equal length. Roentgen examination was advised but was not made until a week later at the urgent insistence of the attending physician. The film was reported as showing "a recent fracture through the left great trochanter at its upper pole. The fragments are in good position." At this time immobilization in a plaster of paris spica was advised. The patient refused to submit to this treatment and continued with his work as house superintendent. Except for physical therapy, no treatment was given. Complete recovery, without any disability, was subsequently reported.

Case 6.—George T., a writer aged 37, was seen on May 28, 1935, the day after his injury. The patient stated that he had fallen from a ladder, landing on his right side and striking his hip. He could not recall all the details, but he believed that while attempting to protect himself in his fall he had "strained his right hip and felt something give way." Though complaining of pain, he was able to rise, to bear weight and to walk into his house with some assistance. He noted that he walked awkwardly and that the right leg seemed suddenly longer than the left. Examination disclosed slight ecchymosis about the great trochanter. There was tenderness in this area on pressure, and the motion of the hip in all directions was limited by pain. The leg was held in slight external rotation, and the tip of the trochanter appeared to be above Nélaton's line. A tentative diagnosis of impacted fracture of the femoral neck was ventured, despite the fact that measurement of the distance between the anterior superior spine of the ilium and the internal malleolus revealed no variation in length between the injured leg and the normal leg. The significance of this apparent paradox was not realized until the roentgenogram (fig. 4) disclosed that the patient had suffered an avulsion fracture of the tip of the great trochanter.

Because of the pain, the leg was immobilized in a plaster of paris spica in the position of abduction and slight external rotation for about eight weeks. On removal of the spica, union was found to be solid, and the patient was able actively to abduct and externally to rotate the leg. After a short period of physical therapy to overcome the stiffness the patient made a complete recovery.

CASE 7.—Opinion in the case of David G., a laborer aged 28, was requested on March 11, 1937, with particular reference to the necessity or advisability of open operation in the treatment of a fracture of the tip of the great trochanter. The patient alleged that while fixing a boiler he had fallen a distance of 3 or 4 feet (38 to 41 cm.) and had landed on a pile of bricks, striking his right hip. He complained of severe pain and inability to walk. He was taken to a nearby hospital, where a roentgenogram showed a fracture of the tip of the great trochanter (fig. 5). The physician in charge suggested immediate operation.

Fig. 4 (case 6).—Typical fracture resembling that in figure 3.

When examined several days after his injury, the patient was found to have no external signs of contusion or abrasion of the skin. There were moderate tenderness on pressure over the trochanter and slight limitation of motion by pain. There was no shortening of the affected leg. Immobilization in a plaster of paris spica with the leg in abduction was recommended. Because of the lack of cooperation on the part of the patient and the subsidence of symptoms, even this measure was not undertaken by the attending physician. Rest in bed was advised but was never carried out. During his waking hours the patient seldom

rested and was frequently out of bed. Nevertheless, recovery was apparently uneventful, and at the end of about three weeks the patient was discharged from the hospital. Some two months later the opportunity for examining this patient in court presented itself. The patient claimed inability to use the leg normally, but careful examination disclosed no limitation of motion, either active or passive.

COMMENT

Several features of this type of fracture stand out significantly. Though there is invariably a history of a fall, it is interesting to note

Fig. 5 (case 7).—Typical fracture resembling that in figure 3.

that there is almost never any evidence of injury to the overlying soft tissues and seldom even any signs of ecchymosis. Moreover, the fact that neither the distance fallen nor the weight of the falling body nor the angle or manner of impact materially modifies the resulting bony lesion is remarkable and seems to suggest the operation of a factor other than external force. This possibility is further emphasized by the roentgenographic appearance of the fracture. Roentgenographically these fractures resemble one another, so that the roentgenogram of any one might, with but slight concessions, be mistaken for that of any of

the others. The area involved is always that portion of the trochanter which projects upward and backward from its line of junction with the neck of the femur. The size of the fragment and even the direction of the line of fracture are, with minor variations, almost identical. There is usually no comminution of the fragment and no depression of the cortex at the site of the alleged impact.

Though most authors have expressed adherence to the belief that these fractures are due to external violence, there is but little autoptic or experimental data on which to base an accurate opinion of the pathology of the condition.[5] It seems extremely unlikely, on the law of averages, that such an invariable clinical picture should be the effect of haphazard unpredictable accident. The appearance of the fracture is so unvarying that it can be conceived of only as the outcome of an etiologic mechanism in which both the force and the point of application are relatively constant. These characteristics accurately define an internal avulsing rather than an external contusing causative agent. Neugebauer[1d] reported a case in which the patient fell on one side and suffered the typical fracture on the opposite side. At first thought it might appear that the action of the powerful gluteal muscles would be the competent producing cause of the fracture. That this may be true of the epiphysial separations of adolescence is indicated by the dissections which Poland reported. On the other hand, the inadequacy of this explanation—indeed its impossibility—in respect to the adult type of fracture is revealed by a closer scrutiny of trochanteric anatomy.

The trochanter is described in general as a quadrilateral prominence at the upper end of the femur, at the junction of the neck and the upper part of the shaft.[6] In adults, the epiphysial line is closed, and the greater part of the trochanter has become so closely united with the femur that there is no line of demarcation between shaft, neck and trochanter, except at the upper pole of the last. In its anterior portion the projection of the trochanter above the level of the neck is minimal. Its posterior half, however, projects considerably above and behind the planes of the femoral neck. This constitutes the posterosuperior angle, triangular and bounded below by the line of fusion with the neck and above and behind by the superior and posterior borders of the trochanter. To the medial surface of this portion of the bone, the external rotators of the thigh, the internal and external obturators, the superior and inferior gemelli and the pyriformis muscle are attached.

5. Ashton, J. H.: Lancet **1**:231, 1875. Clarke, J.: Tr. M. & Phys. Soc. Calcutta **7**:398, 1835. Waechter: Deutsche Ztschr. f. Chir. **8**:104, 1877. Warren, F. W.: Dublin J. M. Sc. **62**:69, 1876.

6. Gray, H.: Anatomy of the Human Body, ed. 22, revised by W. H. Lewis, Philadelphia, Lea & Febiger, 1930.

The lateral surface, quadrilateral in form, is broad, rough, convex and marked by a diagonal impression which extends from the posterosuperior to the antero-inferior angle and which serves for the attachment of the gluteus medius muscle . . .[6a]

In the triangular area above and in front of this diagonal, the gluteus minimus is inserted, while the gluteus maximus is partly attached behind and below at the base of the posteroinferior portion of the trochanter (fig. 6).

Judging from its insertion alone, the action of the gluteus minimus should be the avulsion of the anterosuperior angle; the action of the gluteus maximus should be the tearing away of a portion of the postero-inferior angle, while the gluteus medius, acting either alone or in conjunction with the other gluteal muscles, should tend to avulse the whole trochanter. Since none of these areas is involved in the typical adult fracture, it is apparent that the groups of muscles mentioned cannot be implicated when the responsibility for the condition is assigned.

There remains, then, only the group of the external rotator muscles. Since these are attached to the medial aspect of the posterosuperior angle of the great trochanter, their unopposed action alone can explain the constancy of the fracture line and the tendency of the fragment to be drawn upward, backward and inward in the direction of contraction of the muscle fibers. That this displacement is slight is in all likelihood due to the insertion of the gluteus medius "into the oblique ridge which runs downward and forward on the lateral surface of the greater trochanter." [6b] This line is at right angles to the line of fracture. The consequence is that the insertion of the gluteus medius straddles the fracture line and by its contraction tends to counteract rather than to participate in the displacement of the fragment. It is only when the injury has been sufficient to tear the tendon to the gluteus medius that major separations of the free fragment occur.

Though this interpretation appears to offer a ready explanation of the facts, it has not been accepted by many observers. In the German literature there is talk of an "Abriszfraktur," that is, an avulsion fracture, yet some German authors in their texts have categorically stated that this fracture can occur only as the result of a direct blow. In the French literature, too, Broca is said to have admitted the possibility of avulsion fracture without ever having seen one. The very knowledge that competent observers have expressed doubt as to the importance of muscular action alone suggests the possibility that other factors, such as trauma, may be contributory elements in the mechanism of production. It may be that the fall so frequently associated with this type of fracture establishes a line of cleavage in a crystalline structure that is already

6a. Gray,[6] p. 240.
6b. Gray,[6] p. 473.

stressed by powerful muscular forces. On the other hand, the relation-
ship may be entirely coincidental. Whatever the connection, there can
be no doubt that only on the basis of the primary muscular pull can
the distinguishing features of this fracture be readily explained and
the clinical picture rationally synthesized.

CLINICAL DIAGNOSIS

Apart from the general symptoms—the history of a fall, the diffi-
culty in walking though weight bearing is possible, the tenderness on

Fig. 6.—Side view of the great trochanter. The oblique line along which the
gluteus medius muscle is inserted is shaded light and runs downward and forward
from the posterosuperior angle to the anteroinferior angle. The triangular postero-
superior angle is shaded dark and presents only its lateral aspect. On the medial
aspect, not shown in the photograph, the external rotator muscles of the thigh
are inserted.

pressure over the trochanter. and the pain and limitation of motion in
the hip—there are certain data which have been considered of especial
importance in the establishment of a clinical diagnosis. In cases of
epiphysial separation Kummer [4a] described a shuffling gait. with the
hip held in abduction and extension. which he stated was typical.
Indeed. he particularly stressed the attitude of extension as a sign of

capital importance in differentiating an epiphysial separation from acute coxitis, which, especially in the early phases, it may closely resemble. On the other hand, Thienhaus [7] reproduced a photograph which indicated that in his opinion adduction and internal rotation of the thigh, with flexion of the hip and the knee, are characteristic. After fracture in the adult Betto [8] and Jáki [9] have expressed agreement with Thienhaus that internal rotation and adduction is the position assumed. In this series the attitude was not specifically commented on, though in 2 cases it was recorded that the leg lay in external rotation. Downward tilting of the pelvis on the affected side has been noted by both Betto and Kummer. This position is doubtless of reflex origin and probably results from the necessity for relaxing the spastic muscles in the injured area. Kummer stressed it as the explanation of the apparent lengthening, which several authors have reported in this condition. Betto called attention to the fact that the patient resists passive internal rotation and cannot produce active external rotation. Theoretically, this selective limitation of motion should be a diagnostic aid of some importance. Practically, its value is extremely problematic, since in the acute stage all motions at the hip are interdicted by pain.

Still another sign, which was noted but improperly evaluated, warrants special mention. In case 6 it has been recorded that the trochanter appeared to be above Nélaton's line and that the length of extremities measured from the anterior superior iliac spine to the internal malleolus of the ankle was the same. Normally the tip of the trochanter lies on a line which connects the anterosuperior spine of the ilium with the most prominent point of the ischial tuberosity. In casual daily practice the elevation of the tip of the trochanter above this line, or the shortening of the base of Bryant's triangle, has been taken to imply an associated shortening of the limb, which could be due to any of a number of conditions focused at some point between the iliac spine and the base of the great trochanter. A little reflection, however, will quickly lead to the conviction that this assumption is not necessarily true under either of two sets of circumstances. In the first place, a normal trochanter may appear to be above Nélaton's line if the end points of the line are lower than normal. This may occur, for example, when there has been a fracture or an avulsion of the iliac spine or of the ischial tuberosity, and it need not detain me beyond mere mention. In the second place, the trochanter may appear to be above Nélaton's line if the trochanter itself is the seat of the lesion, even though the position of the line is normal.

7. Thienhaus, C. O.: Ann. Surg. **43**:753, 1906.

8. Betto, O.: Chir. d. org. di movimento **22**:58, 1936.

9. Jáki, J.: Zentralbl. f. Chir. **63**:1169, 1936.

It is apparent, then, that the statement of the position of the tip of the trochanter acquires meaning only when there is a specific statement as to the position of the line in relation to which the trochanter appears elevated. The correct evaluation of the relationship, therefore, involves a careful comparative measurement of the distance from the internal malleolus to the iliac spine and to the ischial tuberosity on both sides. If either of these lengths is less on the affected side than on the normal side and the trochanter is elevated, any one of a number of conditions may be encountered. If the lengths of the limbs are unchanged, however, and the trochanter is elevated, the tip of the trochanter alone must be abnormal.[10] In the presence of tenderness over the trochanter following an alleged injury, the conjunction of signs mentioned indicates an epiphysial separation in an adolescent or a fracture of the trochanter in an adult. When it is present, this sign is pathognomonic. Unfortunately, it is often not elicited (1) because the exquisite trochanteric tenderness precludes accurate palpation of the tip and (2) because the separation of the fragments is often so slight as to be immeasurable under the skin. When the separation is measurable the relative increase in the distance between the tip of the trochanter and the tip of the external malleolus is pathognomonic.

DIFFERENTIAL DIAGNOSIS

In cases in which the aforementioned special signs cannot be elicited, the differential diagnosis is to be made on a careful interpretation of the clinical data and, in the last analysis, on the roentgenographic appearance. The commoner conditions which may simulate fracture of the great trochanter, such as fracture of the neck of the femur, dislocation of its head and inflammatory diseases like coxitis or peritrochanteric bursitis, can usually be readily differentiated. Occasionally, however, one encounters a case like those following, in which even the roentgenogram, if hastily examined, may give rise to an erroneous impression.

CASE 8.—Felix L., a laborer aged 30, was first seen in the outpatient department after a fall and an alleged injury to the left hip and knee. The patient complained of no disability, continued at his work and came for treatment of abrasions about the knee. It was only after several days that he began to complain of gradually increasing pain and progressive limitation of motion at the hip. Examination disclosed marked tenderness on pressure over the trochanter but no sign of external injury. All motions of the hip caused pain. There was no difference in the measurements of the legs, and the relationship of the trochanter to Nélaton's line was not noted. A tentative diagnosis of fracture of the great trochanter was made and a roentgenogram ordered (fig. 7). A casual view appeared to confirm the clinical impression, because of the presence of the triangular shadow constantly seen in cases of avulsion fracture. A more careful examination of the

10. Milch, H.: M. Rec. **147**:229, 1938.

film disclosed that the trochanter was normal in outline but was surmounted by a
second triangular shadow, which was reported as indicating "irregular calcific
deposits adjacent to and above the great trochanter, owing to calcification in the
gluteus tendon." The patient was subsequently aspirated, and the recovery of the
chalky material typical of peritrochanteric, or so-called calcific gluteal, bursitis
confirmed the roentgen diagnosis.

CASE 9.—S. P., aged 40, was seen in the outpatient department in January
1928, when he presented himself for symptoms suggesting pain in the lower part
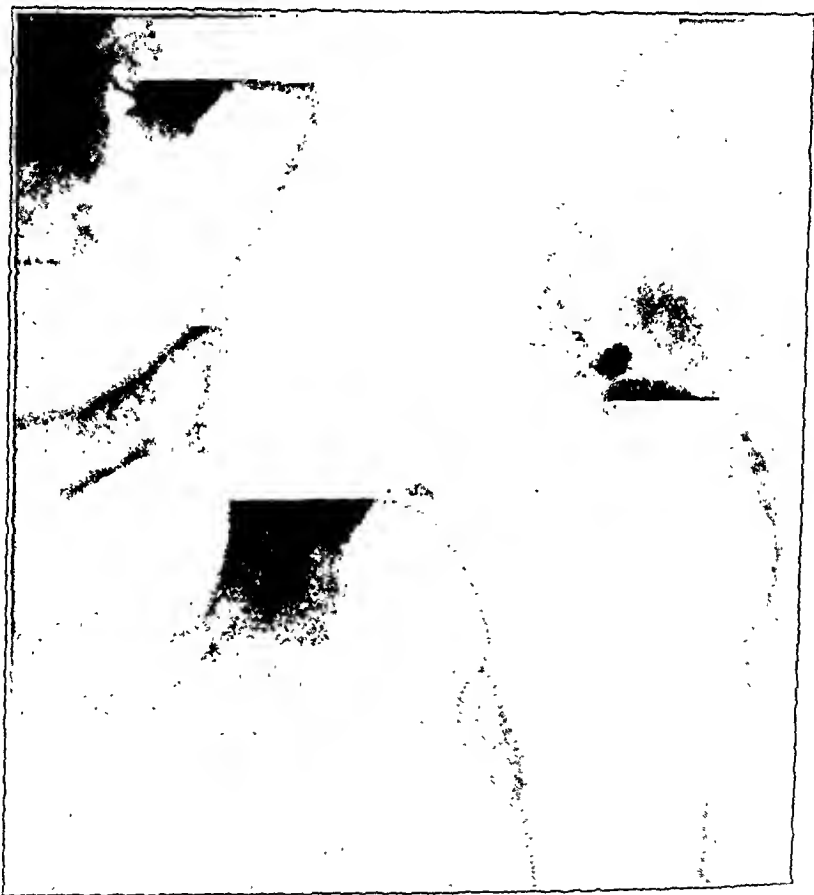
Fig. 7 (case 8).—The faint cockade-shaped shadow lying directly above the
tip of the great trochanter is due to a chalky deposit in the gluteus medius muscle.
The case was one of peritrochanteric or calcified gluteal bursitis. The normal
posterosuperior angle of the trochanter is seen directly below.

of the back. In the course of a routine examination, a roentgenogram disclosed
what appeared to be an old avulsion fracture of the left great trochanter (fig.8).
Although the patient was not complaining of symptoms in the left hip, it was
thought that some slight restriction of motion was present.

An effort at obtaining the history of this injury from the hospital at which
he had been treated previously revealed that about a year before the patient
had been thrown off the back of a truck and apparently had suffered a cerebral

injury, as well as an injury to his left hip. He was given emergency treatment at one of the city hospitals. After four or five days he was discharged to the care of his private physician, who instituted no specific treatment for the injury to the left hip. About six days later he was admitted to the hospital because of pain in the left hip, and at this time a roentgenogram revealed an "old fracture of the great trochanter, with upward and inward displacement of the smaller fragments." The Wassermann reaction was reported as 4 plus. A splint was applied, and the patient was discharged after about three weeks. He apparently received no further treatment.

Fig. 8 (case 9).—Old avulsion fracture of the great trochanter, with moderate displacement and solid union.

TREATMENT

In the matter of treatment little need be said. Healing almost invariably takes place. This is attested by the uncomplicated outcome of numerous operative procedures which involve preliminary cutting of the trochanter. Because the fibers of the gluteus medius prevent excessive separation of the fragments, the patients usually require little more than temporary immobilization with a plaster of paris bandage. To overcome the tension on the avulsing muscles the spica should be applied

with the extremity in abduction, extension and slight external rotation. This is the orthodox treatment. Neglect to immobilize would certainly subject the surgeon to unpleasantness in the event that any inadvertent motion led to excessive separation of the fragments. On the other hand, the evidence afforded by several of the cases reported would indicate that perfectly adequate healing, without any residual disability, may occur even in the absence of any immobilization. Under these circumstances, it is obvious that the question of operative intervention need not arise in the average case. At worst, the indication for surgical suture of the fracture may present itself only in cases of wide separation of the fragments, in which nonunion or muscular atrophy is feared.

SUMMARY AND CONCLUSION

A series of 8 cases of the relatively unusual, isolated fracture of the great trochanter is presented. These cases may be divided into those of epiphysial separation and those of avulsion. Six of the cases of the present series must be classified as instances of avulsion fracture resulting from excessive pull of the external rotator muscles of the thigh. The symptoms are discussed. Elevation of the trochanter in the absence of any change in length of the leg is pathognomonic of the condition. Immobilization is the treatment of choice, even though satisfactory results have been obtained even in cases in which expectant treatment was used. Only in cases in which wide separation of the fragments has occurred are open operation and suture of bone indicated.

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INTESTINAL OBSTRUCTION DUE TO GALLSTONES

REPORT OF TEN CASES

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Intestinal obstruction due to gallstones is a relatively rare condition. In 1890, Courvoisier [1] reported 131 cases, and in 1917 Wagner [2] found reports of 333 cases in the literature. Since that time numerous isolated instances and small series have been reported. During the past ten years, 10 cases have been observed at the University Hospital, constituting 5.3 per cent of all cases of intestinal obstruction.

A large gallstone may enter the lumen of the gastrointestinal tract through the common bile duct or through a fistula between the gallbladder and the bowel. The latter route is the more common. Such fistulas form at the site of inflammatory adherence of an adjacent viscus, usually the duodenum, to the gallbladder. Associated pressure of the gallstone causes necrosis and erosion of the gallbladder and the intestinal walls. Expulsion of the stone into the gastrointestinal tract may occur at the time of formation of the fistula or at any time subsequently.

A correct preoperative diagnosis of this condition is frequently impossible. The symptomatic history of many patients does not point directly to disease of the biliary tract. Furthermore, if the patient has had previously recognized disease of the gallbladder, the early symptoms of obstruction are easily misinterpreted since the pain, nausea and vomiting resulting from obstruction are not unlike the symptoms produced by an acute biliary attack.

Early examination reveals little except tenderness in the upper part of the abdomen. Abdominal distention is rarely noted early, and because most patients with this condition are obese it may not be noted until late in the course of the difficulty. The obstruction may or may not be complete and may be persistent or intermittent.

A plain teleroentgenogram of the abdomen will occasionally visualize the stone. Often, dilated loops of small bowel with many fluid

levels are apparent on the film, so that a diagnosis of obstruction in the small bowel is made.

A reduction of the mortality from this condition can be accomplished only by early diagnosis and operation. In some instances at operation the stone may be crushed within the lumen of the bowel or "milked" distally into the large bowel, but care must be taken that the bowel wall is not injured by the manipulation.

REPORT OF CASES

CASE 1.—Mrs. E. C., aged 49, was admitted to the University Hospital on March 5, 1936, because of cramping abdominal pains and intermittent vomiting during the past eight days. Eight months prior to her present admission a total abdominal hysterectomy and bilateral salpingo-oophorectomy for a carcinoma of the body of the uterus had been performed, followed by an intensive course of irradiation therapy. Except for the carcinoma she had always been in good health until eight days before the present admission, when she noticed a dull pain in the right upper quadrant of the abdomen, with subsequent vomiting and increasing constipation.

Physical examination showed an obese white woman who was acutely ill and moderately dehydrated. Abdominal examination revealed some distention and generalized tenderness. Urinalysis and laboratory examination of the blood, including determination of the blood chlorides, the carbon dioxide–combining power and the urea nitrogen content, all gave normal results.

A diagnosis of intestinal obstruction secondary to neoplastic invasion was made, and conservative treatment was given. On the eleventh day of hospitalization, after the diet had been gradually increased, the symptoms recurred, and an emergency operation was performed. A gallstone 4.5 by 3.5 by 3.5 cm. was found in the ileum. Proximal and distal to this point the bowel was thickened and dilated. In an attempt to explain the dilation and thickening of the bowel distal to the obstruction, a second stone, slightly smaller than the first, was found 15 cm. from the ileocecal valve. The second stone was 70 cm. from the first. Both stones were removed through a single incision in the bowel wall. Palpation of the gallbladder revealed this organ to be adherent to the duodenum. The postoperative course was satisfactory.

Comment.—This case is of interest because of the absence of symptoms suggestive of disease of the biliary tract prior to the present illness and because two stones were present within the small bowel, each causing an independent point of obstruction.

CASE 2.—Mrs. L. S., aged 52, was admitted to the University Hospital on Jan. 24, 1933, because of abdominal pains and vomiting of five weeks' duration. The present illness had started with severe pain in the right upper quadrant of the abdomen. The pain radiated to beneath the right scapula and was diagnosed by her physician as gallbladder colic. She was confined to bed most of the time because of repeated attacks of similar trouble. One week prior to admission there had been severe episodes of vomiting. A recent diagnosis of diabetes mellitus had also been made.

Physical examination revealed an obese, apathetic, irritable, acutely ill woman. The heart sounds were faint; the blood pressure was 110 systolic and 85 diastolic. Distention, generalized rigidity and acute tenderness were present in the mid-abdominal region. On auscultation the abdomen was "quiet."

The erythrocyte count was 5,250,000, the hemoglobin 110 per cent and the leukocyte count 10,200. Examination of the urine showed glycosuria. Determination of the sugar content of the blood revealed 375 mg. per hundred cubic centimeters. The carbon dioxide–combining power of the blood plasma was 44.7 per cent. A diagnosis was made of diabetes mellitus with possibly an acute abdominal condition of undetermined character.

Treatment of the diabetes was instituted, and the patient's condition was improving until the morning of the third day of hospitalization, when she suddenly had severe abdominal pain with increasing symptoms and signs of shock. She died within an hour.

Postmortem examination revealed an obstruction of the small intestine, caused by a gallstone measuring 4.5 by 2.8 by 2.5 cm., which was lodged 20 cm. from the ileocecal valve. There was a recent perforation on the antimesenteric side of the bowel, 15 cm. above the stone. Moderately acute cholecystitis and a cholecystoduodenal fistula 2.5 cm. in diameter were present.

Comment.—This case demonstrates the ease with which severe diabetes may mask an acute intra-abdominal catastrophe and influence treatment.

CASE 3.—Mrs. R. W., aged 72, was admitted to the University Hospital on June 3, 1936, because of generalized abdominal pain, vomiting and obstipation of four days' duration. She had always had good health except for a single attack of gallbladder colic eight years before the present admission.

Physical examination disclosed an obese, dehydrated, acutely ill white woman. The lungs were clear. The heart was somewhat enlarged, with an auricular fibrillation. The blood pressure was 120 systolic and 70 diastolic. There was moderate abdominal distention, with tenderness in the upper part of the abdomen and borborygmus about the umbilicus.

Routine laboratory examinations gave normal results. A teleroentgenogram showed dilated loops of small bowel with fluid levels.

A diagnosis of intestinal obstruction was made, but because of the precarious condition of the patient operation was deferred, and parenteral administration of fluids, continuous gastric suction and enemas were given. Four hours later pulmonary edema suddenly developed, and she died after atropine, venesection and cardiac stimulants had failed to give relief.

At postmortem examination a gallstone 7 by 5 by 5 cm. was observed in the ileum 7 cm. from the ileocecal valve. It had caused complete obstruction. Additional significant findings included a cholecystoduodenal fistula 2 cm. in diameter, pulmonary edema, chronic myocardial degeneration and generalized arteriosclerosis.

Comment.—Except for the single attack eight years previously, there was nothing in the history to suggest the cause of the obstruction.

CASE 4.—Mrs. R. P., aged 30, was admitted to the University Hospital on Aug. 21, 1932, complaining of the classic symptoms of obstruction of the small bowel, which had occurred intermittently for the past eight days, with occasional relief after repeated enemas.

On examination she cooperated poorly, being toxic and acutely ill. There were abdominal distention, diffuse tenderness and borborygmus over the entire abdomen. The routine laboratory examination gave essentially normal results. A plain flap teleroentgenogram revealed the classic picture of obstruction of the small bowel.

With conservative management she made definite improvement for forty-eight hours; then the symptoms increased. An emergency operation was done. A gallstone 5 by 3 by 3 cm. was lodged in the ileum, 10 cm. from the ileocecal valve. It could be easily crushed within the lumen of the bowel and the fragments pushed into the cecum. The gallbladder was adherent to the duodenum and the stomach. Postoperatively her condition became more critical, and she died twenty-four hours later.

Comment.—Because this patient had no history of disease of the biliary tract and was only 30 years old the correct cause of the obstruction was not considered before operation.

CASE 5.—Mrs. C. S., aged 83, was known to have diabetes. She was admitted to the University Hospital on Jan. 21, 1935, complaining of severe, generalized abdominal pains. During the past four years she had had repeated attacks of pain in the right upper quadrant of the abdomen. The attacks had been occurring with increasing frequency and severity, and two days before the present admission after an episode of colic, the pain was localized in the left side of the abdomen and was associated with large emeses. Her physician reported palpating the gallstones the night before her admission; however, the next morning they had disappeared.

Examination showed a thin woman with pinched facies. There were abdominal distention, generalized tenderness and an intestinal pattern. Laboratory examination of the urine and the blood gave normal results except for a leukocyte count of 22,600.

A diagnosis of intestinal obstruction due to a gallstone was made, and at operation a stone measuring 4 by 2 by 2 cm. was found in the midjejunum. It was impossible to crush the stone within the lumen of the bowel. A short incision was therefore made in the wall of the bowel, and the stone was removed. The postoperative course was satisfactory.

Comment.—The unusual feature of the case was the palpation of the stones in the region of the gallbladder prior to the onset of the obstructive symptoms and their disappearance after the onset. It is significant that age is less a factor in mortality than is an early diagnosis.

CASE 6.—Mrs. A. G., aged 67, was admitted to the University Hospital May 12, 1934. For the past three years the patient had had several typical attacks of gallbladder colic. A severe episode had occurred one year prior to her admission to the hospital. Ten days before admission she had recurring attacks of generalized abdominal pain associated with vomiting.

Abdominal examination revealed distention, moderate tenderness and borborygmus in the left upper quadrant. Laboratory examination of the urine and the blood gave normal results. A teleroentgenogram revealed dilated loops of small bowel, with fluid levels and a negative shadow in the right lower quadrant, which was interpreted as representing a gallstone.

After an adequate amount of parenteral fluids had been administered, operation disclosed a gallstone 3 by 2.5 by 2.5 cm. It was situated 14 cm. from the ileocecal valve. An attempt was made to crush the stone within the lumen of the bowel.

but this failed and resulted in sufficient trauma to necessitate creation of an anastomosis between the ileum and the cecum after removal of the stone. On exploration of the right upper abdominal quadrant the fundus of the gallbladder was found to be adherent to the duodenum. Postoperatively a fecal fistula developed, which subsequently closed.

Comment.—An attempt at milking the stone into the colon is justified, but severe injury to the bowel may result.

CASE 7.—Mrs. A. S., aged 50, was admitted to the University Hospital on April 11, 1927, becaues of abdominal pains and vomiting of four days' duration. A diagnosis of diabetes mellitus had been made one year prior to this admission. During the past eleven years she had frequently suffered from a burning sensation in the epigastrium, at times associated with vomiting. With the recent trouble she also complained of obstipation, although occasionally she would pass a small amount of flatus.

The patient was obese, dehydrated and acutely ill. The abdomen was distended, and generalized tenderness was present, especially marked in the right upper quadrant, where a questionable mass was palpable. Examination of the urine revealed glycosuria. The sugar content of the blood was 325 mg. per hundred cubic centimeters. Examination of the blood otherwise gave normal results except for a leukocyte count of 22,000.

A diagnosis of acute cholecystitis was made, and conservative treatment was administered for four days. Because of increasing symptoms and abnormal find- . ings the diagnosis was changed to acute pancreatitis or intestinal obstruction, and exploration was advised.

At operation a gallstone 5.5 by 4 by 4 cm. was found in the second portion of the duodenum. The stone was removed by incision of the bowel, after which a ligature was placed about the pylorus and a posterior gastrojejunostomy performed in the hope of preventing leakage through the duodenal suture line. The patient's death thirty-six hours after the operation was observed at postmortem examination to have been caused by peritonitis resulting from leakage through the duodenal suture.

Comment.—Although the known tendency of duodenal wounds to leak was anticipated and additional surgical procedures were done, this did not prevent a fatal complication.

CASE 8.—Mr. J. S., aged 56, was admitted to the University Hospital on Oct. 2, 1935, because of gastric trouble of five months' duration. During the past two weeks, one-half hour after each meal he had noticed a dull, aching pain and a feeling of fulness in the epigastrium, associated with episodes of vomiting. The vomitus often contained food eaten the preceding day. He had lost 40 pounds (18.1 Kg.) in weight and much strength since the onset of the trouble.

The patient showed evidence of loss of weight and of protracted illness. The abdomen was flat, with moderate tenderness and rigidity in the epigastrium. Laboratory examinations of the urine and the blood gave normal results. Gastric analysis showed seven points of free hydrochloric acid to be present. Teleroentgenographic studies of the gastrointestinal tract revealed a dilated stomach with almost complete obstruction at the pylorus.

A modified Sippy ulcer regimen for thirteen days failed to improve the patient's condition, and a diagnosis of carcinoma of the stomach having been made, laparotomy was performed. In the pyloric region a hard mass 5 cm. in diameter was found. It was tightly adherent to the under surface of the liver, with apparent invasion

about the gallbladder. The mass was smooth, white and so hard that the surgeon felt it was too firm to be a malignant tumor. There was no evidence of metastasis. Material for biopsy was taken from the mass involving the liver, and a posterior gastrojejunostomy was performed. The patient gradually lost ground and died forty-one days later.

Postmortem examination revealed a pericholecystic abscess secondary to a perforation of the fundus of the gallbladder, with a fistula 2 cm. in diameter between the abscess cavity and the first portion of the duodenum. There were gallstones within the gallbladder, within the abscess cavity and directly opposite the fistula, in the lumen of the duodenum. The gallstone in the duodenum was 2.5 cm. in diameter and completely obstructed the lumen of the bowel. Surrounding the area there was an extensive chronic inflammatory reaction without gross or microscopic evidence of malignancy.

Comment.—This case is of particular interest because preoperatively and at operation a diagnosis of malignant tumor of the stomach seemed logical.

CASE 9.—Mrs. A. T., aged 37, was admitted to the University Hospital on Feb. 12, 1936, complaining of recurrent attacks of epigastric pain. In 1925 a cholecystectomy had been performed, the gallbladder having contained numerous small stones and the common duct having shown nothing remarkable. After the cholecystectomy she felt well until one year before the present admission, when she noticed gnawing epigastric distress, aggravated by ingestion of fatty and fried foods and accompanied by much flatulence. She had had fifteen severe attacks of typical gallstone colic, each associated with jaundice, dark urine and clay-colored stools.

The patient on admission did not appear ill, and there was no clinical evidence of jaundice. The abdominal wall was relaxed; there was no muscle spasm and only moderate tenderness to deep palpation in the epigastrium. Laboratory examination of the urine and the blood, including a van den Bergh test, gave normal results.

The day after admission she had a severe attack of colicky epigastric pain accompanied by vomiting, which lasted four hours. A diagnosis of stone of the common duct was made, and she was treated conservatively for six days, with complete relief.

At exploratory laparotomy a round, thin-walled diverticulum measuring 5 cm. in diameter was found. It communicated with the second portion of the duodenum through an opening 2 cm. in diameter just proximal to the ampulla of Vater. The common duct was opened, and no stone or other demonstrable pathologic condition was encountered. Because of the position of the diverticulum in the angle formed by the common duct and the duodenum it was felt this might account for the patient's symptoms of recurrent obstruction of the common duct. The diverticulum was excised and the opening in the duodenum closed.

Postoperatively the patient had an unusual amount of abdominal distention and vomiting, obtaining partial relief by continuous gastric suction. On the sixth postoperative day a duodenal fistula was demonstrated. She continued to vomit intermittently, gradually losing ground and dying on the twenty-fourth postoperative day.

Postmortem examination revealed a fusiform gallstone 6 by 4 by 3 cm. lodged in the small bowel, 23 cm. from the ileocecal valve. It was apparently capable of acting in a ball valve fashion in producing obstruction. The duodenal fistula was well walled off.

Comment.—Explanation of the origin of such a stone in the intestinal lumen is difficult. Large gallstones have been known to be extruded from the common duct. Perhaps in this instance the stone may have been lodged in the duodenal diverticulum and at operation may have been extruded into the duodenum.

Case 10.—Mrs. N. S., aged 59, was admitted to the University Hospital in June 1937, because of severe, intermittent, crampy abdominal pains associated with vomiting of eight days' duration. There was an increasing degree of obstipation, although she had passed some flatus with each daily enema. During the past ten years she had had typical attacks of gallstone colic, and the onset of the present illness was similar to that of the previous episodes.

The abdomen was somewhat distended, with tenderness throughout, especially over the region of the gallbladder. Urinalysis and examinations of the blood all gave normal results.

A diagnosis of subacute intestinal obstruction probably due to a gallstone was made. At operation a globular gallstone 2 cm. in diameter was found 90 cm. from the ileocecal valve, causing obstruction of the lumen of the bowel. The stone could not be crushed or displaced and was removed after the bowel wall had been opened. Palpation of the gallbladder revealed this organ to be adherent to the duodenum. The postoperative course was satisfactory except for a wound infection which delayed her discharge until the thirty-sixth day.

GENERAL COMMENT

In our experience, intestinal obstruction due to gallstones occurs with sufficient frequency to make it an important consideration in the diagnosis of acute abdominal conditions. This is particularly true when the patient has had previous typical gallstone attacks, but this type of obstruction may occur in a patient who has never had such an attack. Clinical diagnosis is likely to be difficult. The factors which make it so are the similarity of the symptoms to those of an acute gallstone attack and the lack of early physical or laboratory findings which would positively indicate the nature of the condition. In our series only 3 such diagnoses were made preoperatively.· In 1 case a diagnosis depended on the disappearance of previously palpable stones in the gallbladder; in another a stone produced a negative filling defect in a flat teleroentgenogram. The diagnosis was made in only 1 case which presented the classic history of previous biliary colic followed by a sudden development of symptoms of acute intestinal obstruction.

We believe that greater alertness in making this diagnosis and more frequent use of the teleroentgenogram will aid in making not only more frequent preoperative diagnoses but earlier diagnoses. While the teleroentgenogram may show only evidences of fluid levels within a dilated bowel, this finding is uncommon except in association with paralytic ileus or mechanical obstruction. In our series, diabetes mellitus was present in 3 of the 10 cases. In 2 instances the diabetes was severe. In no instance, however, was it shown to contribute in any way to the picture produced by the obstructing gallstone.

CONSEQUENCES OF INSTRUMENTAL DILATION OF THE PAPILLA OF VATER

AN EXPERIMENTAL STUDY

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It is common knowledge among surgeons that calculi in the common bile duct are frequently overlooked. Consequently, the common duct is explored at the time of cholecystectomy in an increasing percentage of cases. The exploration is not considered complete unless the patency of the papilla of Vater is proved, and this step is often combined with systematic instrumental dilation of the papilla. The methods used for dilation differ somewhat in the type of instrument and in the amount of distention recommended. The dilators employed have been in most instances either soft woven catheters[1] or metal probes with olive tips (Bâkes).[2] It is the purpose of this paper to describe a series of experiments planned to reproduce as nearly as possible in the experimental animal the conditions of the operation. The immediate and late effects of dilation with both types of instruments have been studied, and the influence of various factors has been evaluated. The clinical significance of these studies has been discussed elsewhere.[3]

Dogs were chosen as experimental animals because the papilla and intramural portions of the common bile duct of the dog more nearly resemble the corresponding regions in man than do those of any other animal commonly used in the laboratory.[4] Although the common bile duct and the pancreatic ducts of the dog open into the intestine separately, there is a musculus proprius two layers thick about the papilla

1. Cheever, D.: Instrumental Dilatation of the Papilla of Vater and the Dislodgment of Calculi by Retrograde Irrigation, Arch. Surg. 18:1069-1077 (April) 1929.

2. Allen, A. W., and Wallace, R. H.: Technique of Operation on the Common Bile Duct, Am. J. Surg. 28:533-561, 1935.

3. Zollinger, R.; Branch, C. D., and Bailey, O. T.: Instrumental Dilatation of the Papilla of Vater, Surg., Gynec. & Obst. 66:100-104, 1938.

4. Boyden, E. A.: The Sphincter of Oddi in Man and Certain Representative Mammals, Surgery 1:25-37, 1937.

and the intramural portion of the duct (fig. 1). In the dog, Boyden [4] found that almost the entire intramural course of the bile duct is encircled by scattered loops of smooth muscle. The most distal of these loops he found to be thicker and more isolated than the rest. Hence he felt that these muscles may be regarded as a subterminal sphincter choledochus, or subterminal ring. Lueth [5] in studying the intramural pressure gradient of large, anesthetized dogs described a special sphincter

Fig. 1.—Normal papilla of Vater of a dog (× 13) showing intact layers of musculature distinct from that of the duodenal wall. (Reproduced by permission of *Surgery, Gynecology and Obstetrics*.)

of the papilla which exerted one third to one sixth of the total resistance offered to the flow of fluid through the intramural portion of the common bile duct. He called attention to the bulging of the papilla before the threshold level at which fluid flowed into the duodenum was reached. He regarded this as evidence of a true terminal sphincter. We have

5. Lueth, H. C.: Studies on the Flow of Bile into the Duodenum and the Existence of a Sphincter of Oddi. Am. J. Physiol. **99**:237-252, 1931.

seen this to be a constant finding in procedures for determining ductal and perfusion pressures during operations in which the duodenum has been opened.

METHOD

Experiments were carried out on 63 dogs for the purpose of studying the effects of various procedures on the biliary system. In one group the papilla of Vater was dilated through the stump of the cystic duct, while in the remaining groups it was dilated by the transduodenal approach. Because of the relative size of the cystic and common bile ducts in the dog it is impossible to pass an instrument sufficiently large to dilate the papilla to the desired extent. Since it has long been established that cholecystectomy causes some dilatation of the ductal system, it was thought advisable to carry out certain of these procedures with and without cholecystectomy in order to determine how important a role cholecystectomy itself played in the production of the final results. The size of the papilla of Vater in normal dogs varies to some extent with the size of the animal. We have accepted a diameter equal to that of a no. 10F catheter as representative of the average size for the large dogs used in this laboratory.

In most cases, at the time the dogs were killed, roentgenograms were taken after injection of iodized oil into the biliary tract. This was done in order to determine the amount of dilatation of the ductal system that took place after the various operative procedures. Figure 2 shows a normal biliary tree as outlined in this way. Attention is called to the fine radicles, which are the intrahepatic ramifications of the system. Only a few of these radicles are filled with the injection mass in this normal specimen.

Histologic studies were made in all instances. Changes were sought in the papilla of Vater, in various portions of the common bile duct, in the extrahepatic ducts and in the intrahepatic ductal system. The appearance of the liver at the time the animal was killed was compared with that of tissue taken for biopsy at the time of operation.

GROUP 1.—*Cholecystectomy alone.*

As has been mentioned, cholecystectomy alone has long been known to cause a certain amount of dilatation of the extrahepatic ductal system. In order to determine the extent of this factor under the conditions of our experiments, we performed cholecystectomy on 6 dogs. Biopsy of material from the liver was done at the same time in order that the tissues taken for biopsy might later be compared with that obtained at postmortem examination. The dogs were killed one hundred and twenty days after operation. Grossly there had been slight dilatation of the papilla of Vater and of the extrahepatic ductal system. The size of the papilla was found to average the size of a no. 14F catheter, and that of the common bile duct, that of a no. 19F catheter. A roentgenogram (fig. 3) taken after injection of iodized oil into the biliary system confirmed the enlargement of the common bile duct. Note the bulbous dilatation of the remnant of the cystic duct, indicated by the arrow. There was, however, only a slight increase in size of the larger intrahepatic ducts. The terminal ones appeared much the same as in the normal control animal. Microscopic examination showed some flattening of the villi of the common bile duct. There was no inflammatory reaction in the region of the common bile duct or the papilla of Vater. Specimens for biopsy taken from the liver at the time of cholecystectomy and those obtained at the time the animal was killed were normal in appearance.
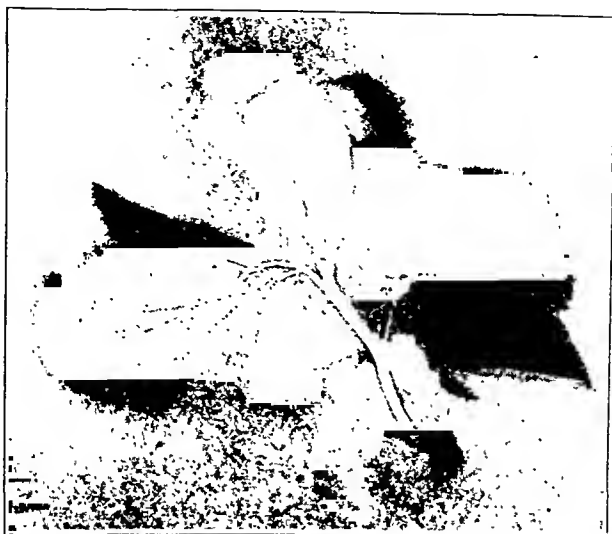
Fig. 2.—Roentgenogram of the biliary tree of a normal animal after injection of iodized oil.
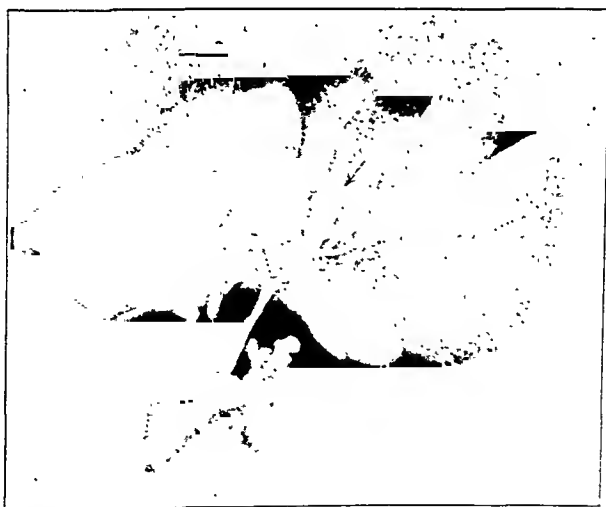
Fig. 3.—Roentgenogram showing slight dilatation of the intrahepatic ducts of an animal after cholecystectomy. The arrow points to the bulbous remnant of the cystic duct.

Fig. 4.—Roentgenogram showing the effect of cholecystectomy followed by dilation of the papilla through the cystic duct. Note the extreme dilatation of the extrahepatic system.

Fig. 5.—Photomicrograph ($\times$110) of the common duct of an animal in which dilation was done through the cystic duct. The villi are flattened, and there is increased connective tissue with no evidence of inflammation.

GROUP 2.—*Cholecystectomy: dilatation of the papilla through the cystic duct.*

In this group an attempt was made to dilate the papilla of Vater through the stump of the cystic duct after cholecystectomy. Seven dogs were used. Obviously it was impossible to dilate the papilla greatly without damaging or tearing the common bile duct beyond repair. In 2 of the dogs, the catheter introduced was no. 16F. In the remainder, no. 14 or no. 12F was used. The animals were killed on an average of one hundred and twenty-five days after this procedure. The papilla was found to be enlarged slightly (to the diameter of a no. 14F catheter on the average). An unexpected finding was the extreme dilatation of the extrahepatic ducts. This was more marked than in any other group in the series. The average diameter of the common bile duct was equivalent to that of a no. 28F catheter. Roentgenograms taken after injection of iodized oil into
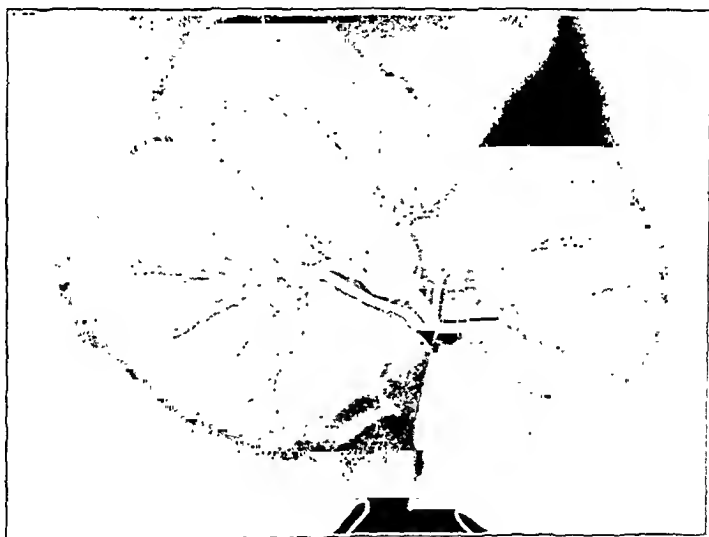
Fig. 6.—Roentgenogram showing generalized increase in the size of the ductal system following transduodenal dilation by catheter.

the biliary system confirmed the striking dilatation of the common and extrahepatic bile ducts (fig. 4). There was slight enlargement of the larger intrahepatic ducts and of the terminal radicles. Microscopic examination showed some dilatation of the papilla; there were thickening and fibrosis of the wall of the common bile duct (fig. 5). The lining of the common duct was greatly flattened, although in some regions a few villi persisted. Biopsy of specimens taken from the liver at the time of operation showed normal tissue. Autopsy specimens of the liver showed a slight increase in the periportal connective tissue, and moderate numbers of lymphocytes were found in that region.

GROUP 3.—*Cholecystectomy: transduodenal dilation of the papilla with catheters.*

In this group there were 7 dogs. Cholecystectomy was followed at the same operative session by transduodenal dilation of the papilla to the no. 18F size

by means of soft woven catheters. Biopsy of material from the liver was done in each instance. After an average of ninety-six days the dogs were killed. At this time there was some dilatation of the extrahepatic ductal system, with slight thickening of the walls. The roentgenogram (fig. 6) demonstrated only slight increase in the size of the larger ducts. In this specimen the stump of the cystic duct was strikingly dilated. An increase in the number of visible intrahepatic radicles was noted, and all appeared slightly larger than normal. The papilla of Vater was found to have returned to the size of a no. 10F catheter on the average, and the common bile duct had increased in size to that of a no. 21F catheter. Microscopic examination showed an increase in connective tissue about the papilla. In the common bile duct the villi were flattened, and there was slight increase in fibrous tissue, but no inflammatory reaction was noted. Biopsy specimens taken from the liver at the time of the operation were normal. Those obtained at the time of the animals' death showed a slight increase in the periportal connective tissue. The microscopic sections also demonstrated the dilatation of the intrahepatic bile ducts indicated by the roentgenograms.

Fig. 7.—Roentgenogram showing an increase in size of the intrahepatic ducts with slight increase in size of the extrahepatic system following dilation with metal dilators.

GROUP 4.—*Cholecystectomy; transduodenal dilation of the papilla with Bâkes dilators.*

A group of 5 dogs was used to study the effects of the Bâkes dilators on the biliary system. Cholecystectomy was carried out; then the duodenum was opened, and the papilla of Vater was dilated transduodenally with the Bâkes instruments to a diameter equal to that of a no. 17F catheter. On an average of sixty-three days after the operation the animals were killed. It was found that the papilla had returned to approximately normal size, the average being equivalent to that of a no. 12F catheter. The diameter of the common duct at this time was found to be that of a no. 16F catheter. A roentgenogram (fig. 7) taken after injection of iodized oil showed some enlargement of the extrahepatic system as well as an increase in the number of small intrahepatic ducts which were demonstrable

after the injection. There were also an enlargement of the larger intrahepatic ducts and an apparent clubbing of their terminal injected portions. Microscopic examination showed changes similar to those in the preceding group. There were slight scarring in the region of the papilla of Vater, flattening of the villi in the common bile duct and a minimal increase of periportal connective tissue in the liver.

GROUP 5.—*Cholecystectomy; dilation of the papilla with Bakes dilators; drainage of common bile duct.*

In an effort to simulate in another respect the procedure usually carried out in man, the common bile duct was drained in 4 animals. After cholecystectomy had been performed a catheter was introduced into the common bile duct through the stump of the cystic duct and was anchored firmly in place. The duodenum was then opened, and the papilla of Vater was dilated with the Bakes dilators to the diameter of a no. 21F catheter. After ninety-two days the animals were killed. It was found that the diameter of the papilla was equal to that of a no.

Fig. 8.—Roentgenogram of an animal in which the common duct was drained after cholecystectomy. Dilation was carried out by transduodenal approach. Generalized, though slight, ductal dilatation is present.

11F catheter on the average. There was inflammatory reaction about the common bile duct in all of the animals, but there was no evidence of compression or stricture of it. A roentgenogram (fig. 8) taken after injection of iodized oil showed a definite increase in size of the extrahepatic bile ducts but only a very slight increase in size of the intrahepatic ducts. The microscopic appearance of the papilla and intramural portion of the duct in most places did not vary from the normal, and there was only slight scarring in a rare field. The common bile duct was dilated; the villi were flattened, and there was a considerable increase of connective tissue with lymphocytic infiltration. The liver showed slight increase in periportal connective tissue, but there were no inflammatory changes.

GROUP 6.—*Cholecystectomy; dilation of the papilla after an interval.*

This group was studied in order that dilation of the papilla of Vater might be carried out in a biliary system already rendered pathologic by the preceding

operation. Multiple operations on the human biliary system are by no means rare. This was designed as a test to see whether such operations produce more marked effects than do similar procedures when carried out at one operation. Cholecystectomy was performed as a preliminary operation on a series of 6 dogs. Two hundred days after the original procedure the papilla was dilated transduodenally so that the average diameter was that of a no. 20F catheter. The animals were killed one hundred days after the second operation. It was found that the papilla had returned on an average to the diameter of a no. 12F catheter. There was a slight increase in the size of the common bile duct and of the intrahepatic ducst, as seen in the roentgenograms. Slight scarring was present in the intramural portion of the ductal system. There was flattening of the villi in the common bile duct.

GROUP 7.—*Cholecystectomy; dilation of the papilla; redilation after an interval.*

With 5 animals dilation was performed on two occasions. This was done in order to determine the effects of a second dilation on a papilla which had had previous trauma. The procedure in this group was an extension of that used in group 6 so that the second operation was performed on an extrabiliary system already altered by the first dilation as well as by .the cholecystectomy. At the first operation cholecystectomy and biopsy of material from the liver were performed. At the same session the papilla of Vater was dilated to an average size equal to that of a no. 17F catherter. This was done by means of a soft woven catheter by transduodenal approach. One hundred and forty days after the first operation a second operation was carried out. The duodenum was again opened. The papilla of Vater at this time was found to have returned to the normal size (that of a no. 10F catheter) ; it was then dilated to the no. 20F size. When the animals were killed, one hundred days after the second operation, the papilla was found to be somewhat enlarged, measuring the same as a no. 14F catheter on the average. The common bile duct in all instances showed gross evidence of inflammatory reaction. Its average diameter was that of a no. 23F catheter. A roentgenogram (fig. 9) of the biliary system showed the extrahepatic ducts to be greatly enlarged in 4 dogs but not in the fifth. In this animal they were thick walled, and there was considerable stenosis of the duct in its midportion. On the whole, roentgenograms demonstrated an increase in size of the intrahepatic ducts, particularly in the medium-sized ones. The injected intrahepatic ducts were also more numerous than in control animals. Microscopic examination in each instance showed considerable alteration in the region of the papilla of Vater. The normal contours of the muscle bundles were broken up and the intervals filled with dense but well vascularized collagenous tissue. No areas of recent hemorrhage were seen. There were some phagocytes filled with hemosiderin granules in scattered areas. The common bile duct in each case showed dilatation and flattening of the villi. There was moderate lymphocytic infiltration and increase in connective tissue in both the submucosa and the muscularis. Comparison of the biopsy specimens taken from the liver at the first operation with sections obtained after death of the animal showed an increase in the periportal connective tissue. This was accomplished by lymphocytic infiltration and a deposit of hemosiderin in phagocytes in that region. The small intrahepatic ducts were all dilated, but the degree of dilatation varied considerably from specimen to specimen.

GROUP 8.—*Dilation of the papilla without previous cholecystectomy.*

Since it had been shown by previous investigation that there is an enlargement of the papilla of Vater and the common bile duct after cholecystectomy

alone, dilation of the papilla of Vater was carried out with a group of 8 dogs on which no previous operation had been performed. Catheters were used for dilation in 5 dogs, the papilla being dilated transduodenally to a diameter equal to that of a no. 21F catheter. The Bâkes instruments were used in 3 dogs, dilation being carried to the no. 23F size. The animals were killed at intervals varying from one hundred and twenty to one hundred and sixty days after the operation. It was found that the papilla had returned to the diameter of the no. 10F catheter. The common bile duct in all instances presented enlargement, averaging in diameter the size of a no. 20F catheter. Roentgenograms taken after injection of iodized oil showed slight enlargement of the extrahepatic ducts, but there was very little increase in size of the intrahepatic ductal system. With some of these dogs the biliary system presented a nearly normal appearance, the type of instrument used for dilation apparently having no effect on the final result. Microscopic examination showed only slight scarring of the papilla, several of the sections appearing normal. There was some slight dilatation of the

Fig. 9.—Roentgenogram of the biliary tract of an animal in which the papilla was dilated on two occasions. There is an increase in size of the extrahepatic and larger intrahepatic ducts.

common bile duct, and scarring of its wall was minimal. The villi were still visible, though less prominent than normal. In an occasional field there was slight increase in the periportal connective tissue of the liver. Occasional lymphocytes were present in this region, and some slight enlargement of the terminal bile ducts could be detected.

GROUP 9.—*Experiments to show the early effects of dilation of the papilla.*

The early effects of dilation of the papilla were studied in a group of 15 dogs. Dilation was carried out with soft woven catheters by the transduodenal approach. Cholecystectomy was not performed. The dogs were killed at intervals varying from one to twenty-eight days. Gross examination at the time of death showed that in the first week the papilla was large and edematous, protruding into the lumen of the duodenum. No attempt was made to measure the actual

size in order to obtain microscopic sections of papillae which had had no other trauma than that occurring at the time of the original dilation. In the specimens obtained one to three days after dilation the continuity of the epithelium was broken in many places, and these areas were sealed with fibrin and polymorphonuclear leukocytes. The exudate was so extensive as to fill the lumen almost entirely (fig. 10). In addition, there were extensive areas of hemorrhage in the surrounding tissue. Portions of the mucosa which were not eroded showed edema and infiltration with polymorphonuclear leukocytes. At the end of a week the lumen of the papilla had reached approximately normal size, and most of

Fig. 10.—Photomicrograph (× 90) of the papilla of Vater three days after dilation. The lumen is filled with fibrin and leukocytes. The mucosa is interrupted, and there is acute inflammatory reaction beneath it. (Reproduced by permission of *Surgery, Gynecology and Obstetrics*.)

the exudate had disappeared. The continuity of the epithelium was partially restored. In the mucosal stroma there were many lymphocytes, but polymorphonuclear leukocytic reaction was slight. There were many young fibroblasts and some newly formed capillaries throughout the mucosa and in the layers of muscle ensheathing the papilla. Sometimes these even extended into the adjacent intestinal musculature for a short distance. At the end of one month, connective tissue richer in collagen had taken the place of the fibroblasts. It extended at various points through the investing musculature for a short distance. The mucosal

epithelium was complete, but the glands appeared somewhat altered in outline, and in the stroma about them were numerous lymphocytes and some plasma cells.

<center>COMMENT</center>

The series of experiments on these 63 dogs forms a basis for discussion of the results of various manipulations on the biliary system. The results in the various groups offer evidence which may promote understanding of the results of different types of surgical procedures. Dilation of the papilla of Vater was accomplished through the stump of the cystic duct and also by the transduodenal approach. When it was carried out through the stump of the cystic duct, a large amount of dilatation of the extrahepatic ducts was found at the time of the animal's death. The trauma from instrumentation at the time of operation in this group must have caused considerable damage to the lining of the common bile duct, for sections showed rather extensive scarring. Whether this was due to trauma to the interior of the duct alone or whether injury to the nerve supply of the duct as a result of the dilation was an added factor can not be determined from these experiments. At least, one can be certain that the scarring was localized to the region of the trauma. The papilla of Vater and the intrahepatic ducts appeared both grossly and microscopically normal at the end of one hundred and twenty-five days.

In the remaining groups of experiments, dilation was performed after the duodenum had been opened. The amount of scarring in the region of the papilla and the effect on the other portions of the ductal system varied considerably. In one group there resulted severe damage which could be attributed only to the dilation. This was group 7, in which dilation was performed on two occasions. Uniform and extensive scarring of the region of the papilla with pathologic change in the other portions of the biliary system was a constant finding. There was a definite increase in the periportal connective tissue of the liver. The amount of scarring in the various groups did not seem to be affected by the type of instrument used. Much the same results were obtained with the soft woven catheter as with the metal bougie (Bâkes instrument). The findings in group 5 (in which the common duct was drained by a catheter) were of especial interest. In spite of some inflammatory reaction about the common bile duct there was only slight dilatation of the extrahepatic ducts, and the villi, though flattened, were distinct in most sections. The remaining portions of the ductal system were likewise essentially normal in appearance. This would suggest that drainage of the common bile duct has little permanent deleterious effect on that structure or on other parts of the extrahepatic biliary passages and may, indeed, through reduction in pressure caused by the

block at the papilla immediately following the trauma of dilation, actually be a factor in preventing permanent increase in the size of the ductal system.

In the dogs which showed extensive scarring in the region of the papilla a definite increase in size of the intrahepatic ducts was also observed. This would suggest an increased intraductal pressure.

In the group in which the animals were sacrificed from one to twenty-eight days after dilation of the papilla there can be no doubt that the edema and exudate caused considerable obstruction of the papilla. The edema subsided at the end of approximately a week, and the papilla returned to normal size. Thus, during this period, it is doubtful whether dilation could result in any increase in the lumen of the papilla of Vater unless there had been extensive tearing of the entire intramural portion of the duct. Then there would exist a free

Instrumental Dilation of the Papilla of Vater

Type of Experiment	No. of Animals	Survival, Days	Papilla Dilated to	Size of Papilla
Control	..	...	....	10 F
Cholecystectomy	6	120	....	14 F
Cholecystectomy; dilation through cystic duct	7	125	14 F	14 F
Cholecystectomy; catheter dilation	7	96	18 F	10 F
Cholecystectomy; Bakes dilation	5	63	17 F	12 F
Dilation; common duct drainage*	4	92	21 F	11 F
Dilation 200 days after cholecystectomy	6	100	20 F	12 F
Dilation 140 days after primary dilation*	5	100	(1) 17 F (2) 20 F	10 F 14 F
Dilation without cholecystectomy	8	140	22 F	10 F
Acute experiments	15	1-28	22 F	

* Cholecystectomy also performed.

communication with the duodenum, devoid of a sphincteric mechanism. Such an extensive laceration of this region might allow the entrance of bacteria into the tissues and lead to infection of the region. It would ultimately result in scarring, and stricture might result if contraction were sufficiently great. At any rate, the physiologic action of this region would be interfered with to a great extent by this procedure.

From the standpoint of the surgeon, the purpose in dilating the papilla of Vater extensively is to render its lumen larger so that unnoticed calculi may pass spontaneously.[3] The results of these experiments suggest that shortly after operation the lumen fills with exudate if the papilla has been dilated to a large size. This was confirmed by our studies of intraductal pressure, reported elsewhere.[3] Furthermore, the experiments indicate that when this stage passes the lumen returns to its original size regardless of the extent to which it was dilated at operation. Thus, extensive dilation of the papilla does not enlarge the lumen either shortly after operation or later.

CONCLUSIONS

1. Obstruction of the papilla of Vater after its dilation occurs during the first week as a result of the exudate in the duct and the edema of the surrounding tissues.

2. A certain degree of scarring in the region of the papilla of Vater occurs after extensive dilation. This was moderate to marked in 50 per cent of the experimental animals in the present series.

3. Dilatation of the extrahepatic bile ducts occurred to some extent in all groups. This seems to be influenced by the amount of scarring about the papilla rather than by the method or instrument used.

4. Dilatation of the extrahepatic bile ducts seems somewhat lessened when drainage of the common bile duct is instituted.

5. When portions of the cystic duct are left at cholecystectomy, they dilate to form a pocket of considerable size.

6. Increase of periportal connective tissue and dilatation of the intra-hepatic bile ducts were both proportional to the degree of scarring of the papilla of Vater.

7. The size of the papilla of Vater after dilation by various methods remains essentially the same as the initial size. Dilation thus results in no permanent enlargement of the papilla of Vater.

8. These investigations lend support to the view that no further dilation of the papilla of Vater should be carried out in human patients after its patency has been ascertained.

CORRECTION

In the article by Dr. Deryl Hart entitled "Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy: Results in over Eight Hundred Operations," in the December issue (ARCH. SURG. **37**:956, 1938), in the third sentence of the paragraph beginning "This report," at the top of page 957. "The operations in the present series" should have read "The latter operations;" i. e., the operations referred to are those in which there was a potential source of infection.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Anomalies.—Jasienski[1] called attention to a case in which there was congenital aplasia of the left kidney, the organ being minute and functionless, while the right kidney was an enormous hydronephrotic sac with a large calculus in its pelvis. At necropsy the aplastic organ was found to contain no trace of renal tissue; the entire structure was composed of a series of cystic cavities filled with yellowish serous fluid. Congenital renal aplasia or hypoplasia of such high grade as to deprive the kidney of all functional value is rather rare. Although Ballowitz (1895) collected 213 and Gerard (1905) 278 cases among 527 congenital malformations of the kidney, it is probable that in a great many of these cases the true condition was solitary kidney or double kidney or that the two kidneys were fused on the same side.

It is frequently impossible, especially if necropsy is not performed, to know whether the condition under observation is congenital aplasia, hypoplasia of high grade or secondary atrophy of a kidney. Frequent references in the literature stress the importance of removing a func-

1. Jasienski, G.: Contribution à l'étude des affections du rein unique; un cas d'hydronéphrose calculeuse géante chez un sujet avec atrophie du rein opposé, J. d'urol. **45**:45-50 (Jan.) 1938.

tionless kidney, but mention is seldom made of diseases of the opposite kidney (properly called a solitary kidney), their frequency, their evolution and their outcome. Not infrequently evidence is found that solitary kidneys have been removed. In cases in which functional examination and ureteral catheterization do not give adequate information there is good reason to follow Rovsing's advice to perform exploratory lumbotomy not only when it is uncertain which kidney is affected but when it is impossible to exclude with certainty the possibility of hypoplasia of one kidney. Among the 213 cases of aplasia or hypoplasia collected by Ballowitz the opposite kidney was reported to be of increased size in 55 cases, and in 25 cases chronic nephritis or hydronephrosis was observed. In 16 cases hydronephrosis was due to stone in the kidney or ureter.

It is evident that in such cases obstruction of the ureter by a stone or by a kink due to compression by a large cyst is necessarily followed by fatal anuria and uremia. In the author's case anuria was the final result of a stone in the distended renal pelvis, which from time to time, with changes of position, caused obstruction by its weight. The astonishing thing was that the 26 year old patient lived as long as she did without urinary disturbances. The case shows what minute vestiges of renal parenchyma may suffice to maintain life.

Roentgen evidence of absence of a kidney may indicate previous surgical removal, renal destruction resulting from disease or congenital absence; the remaining kidney, therefore, may be regarded as either a congenital or an acquired solitary kidney.

Braasch and Merricks [2] review the clinical findings in 27 cases of proved renal agenesia (operation, 14; necropsy, 13) and in 42 cases in which the diagnosis was inferred from roentgenographic and cystoscopic data. These findings were compared with those in cases of acquired solitary kidney. The most common subjective symptom of renal agenesia was pain on the side on which the kidney was present. The most common objective evidences found on physical examination were a palpable mass on the side on which the kidney was present (24 per cent) and tenderness to palpation (16 per cent).

As might be expected with renal anomalies, secondary complications were present in the congenital solitary kidney in 43 of the 69 cases. In order of frequency they were pyelonephritis, anomalies of form and position, hydronephrosis, lithiasis, nephritis and tuberculosis.

From roentgenographic data the size and position of the kidney, the size of the renal pelvis and the width and definition of the psoas

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2. Braasch, W. F., and Merricks, J. W.: Clinical and Radiological Data Associated with Congenital and Acquired Single Kidney. Surg., Gynec. & Obst. **67:** 281-286 (Sept.) 1938.

muscle were noted and compared with similar observations in 33 cases of acquired solitary kidney. It was found that the congenitally solitary kidney is enlarged in 90 per cent of cases and that this enlargement is present more frequently and is distinctly greater than in cases of acquired solitary kidney. Enlargement of the pelvis of the congenitally solitary kidney was not commensurate with that of the parenchyma; the size differed little from that of the pelvis of the acquired single kidney. The congenitally solitary kidney tends to occupy a position lower than that taken by the kidney which undergoes compensatory hypertrophy after nephrectomy, and this sign may be regarded as a definite factor in identifying this condition. The shadow of the psoas muscle was wider on the side on which the kidney was absent than on the other side in 16 per cent of cases of agenesia; of 100 consecutive urograms, the shadows were of equal width in 99. A more common finding in cases of agenesia was absence of definition of the psoas shadow on the side on which the kidney was absent (40 per cent). There was a difference in definition on comparison of the two sides in only 16 per cent of a series of 100 unselected urograms.

Stone.—Grosperrin [3] on the basis of 2 illustrative cases of lithiasis associated with tuberculosis of long standing stated that tuberculosis has a marked effect on calcium metabolism, leading invariably to more or less violent decalcification, revealed by increase of calciuria. It is normal for urine rich in calcium salts to have a tendency to deposit these in the form of concretions. Although hypercalciuria is not of any special pathologic importance in every case of tuberculosis, it has marked significance in cases in which tuberculosis has attacked the skeleton.

In the first case reported the lithiasis did not appear until six years after the first symptoms of Pott's disease. While it is impossible to say with certainty whether the mild infection (bacteriuria rather than pyuria) preceded or followed the formation of stone, the friability of the calculus and its granular appearance suggested secondary lithiasis and permitted, with some degree of probability, incrimination of the infection.

On the other hand, uric or uratic lithiasis, such as was present in the author's second case, seemingly develops by a different humoral mechanism. In this case the patient was suffering with florid pulmonary tuberculosis of slow evolution, and nothing in the bony portion of the skeleton indicated any noteworthy decalcification. Yet he was suffering with attacks of renal colic and hematuria and was found on examination to have a small calculus in the left renal pelvis, for which operation

3. Grosperrin: La lithiase rénale chez les anciens tuberculeux, J. d'urol. 45: 199-204 (March) 1938.

was performed. Grosperrin raised the medicolegal question whether a renal stone discovered some years afterward in a case of arrested tuberculosis should be regarded as the result of tuberculosis. An increasing number of cases seems to indicate that there is a clear relation of cause and effect between tuberculosis, with its necessary treatment by superalimentation, and renal lithiasis.

The immediate results of the "V" type of nephrotomy, described by Prather [4] in 1934, proved to be satisfactory. He reviewed the condition of the patients, and particularly of the kidneys, after several years to see if the results justified the procedure.

The follow-up data on 6 kidneys operated on approximately three to five years before justified their being regarded as a group and allowed certain conclusions to be drawn. All of the 5 patients were in good general health. None had pain or symptoms referable to the side on which operation was done.

Stones had not formed in the opposite kidney after operation. Marked recurrence of stone had taken place in 2 of the 6 kidneys which had been operated on. The p_H of urine from 1 kidney, in which recurrence of stone was extensive, was 8.

Four of the 6 kidneys were known to have been infected before operation. Of the 4 kidneys in which there was little or no recurrence of stone, in 2 there was no infection and in the other 2 mild bacilluria without pus. The p_H of the urine from 2 of those kidneys which had remained free of stone was given as 5.5 and 7.0 respectively.

None of the patients had followed an adequate medical program for stone since operation. Prather expressed the belief that with increased interest and knowledge regarding the formation of stone and prevention of recurrence and with intelligent application of the newer urinary antiseptics, results of renal surgical procedures for stone should be definitely improved.

Higgins [5] reviewed 100 cases of recurrent renal lithiasis and stressed the necessity of a conscientious postoperative regimen.

The left kidney was the site of recurrence in 40 cases and the right in 32. Recurrence was bilateral in 28. Recurrence developed most frequently in the first three years after operation in the cases in which recurrence was unilateral and in the first eight years after operation in the cases in which recurrence was bilateral. Staphylococcus albus was the organism most frequently associated with recurrence; the organism next most frequent was of the genus Proteus.

4. Prather, G. C.: Review of the "V" Type Nephrotomy for Staghorn Calculus with Special Reference to Final Results, Am. J. Surg. **39**:589-601 (March) 1938.

5. Higgins, C. C.: Recurrent Renal Lithiasis: Review of One Hundred Cases, Tr. Southwest. Br. Am. Urol. A., 1937, pp. 2-10.

Deficiency of vitamin A was indicated by a positive reaction to the biophotometer test in 68 to 72 per cent of cases.

Nephrectomy was performed in 22 per cent of cases because of poor function or marked destruction of the kidney. Two hundred and twenty-three operations had been performed on this group of 100 patients with recurrent lithiasis of the upper part of the urinary tract.

Bailey and Eberhart [6] briefly reviewed the 8 cases in which renal calculi have been reported to weigh more than 300 Gm. The largest surgically removed stone weighed 1,440 Gm. In Bailey and Eberhart's case nephrectomy was performed with considerable difficulty. The stone weighed 1,565 Gm. Chemical analysis of the stone revealed calcium, magnesium, phosphates, carbonates and a trace of sulfur and oxylates. There were no urates. The patient recovered from the operation.

Von Illyés [7] stated that in cases of bilateral renal stone and in cases of solitary kidney, operation should not be delayed until renal insufficiency has developed, or, if it does develop, operation should be carried out while the insufficiency is in progress. The earlier the operation is performed, the more renal parenchyma can be saved.

Even in the presence of the most extreme involvement every detail of the patient's condition should be considered and the need for surgical intervention determined. Renal insufficiency in cases of desperate involvement can be bettered only by removing the stone which is causing the obstruction and infection. Nonoperative treatment usually eventuates in death of the patient.

Chaton [8] reported a case in which transperitoneal extraction of a calculus from one pelvis of a horseshoe kidney was effected. The first roentgenogram in this case (hematuria was present) resulted in a diagnosis of probable calculus of the right renal pelvis; the kidney therefore was approached by the usual lumbar incision. The organ was found in a position abnormally oblique from above downward and from without inward. The lower pole was astride the vertebral column. The internal contour of the kidney could not be made out, and it became apparent that the organ was continuous, across the median line, with the parenchyma of the other kidney. A diagnosis of horseshoe kidney was made. Débridement in the region of the pedicle, which was displaced in the median portion, was difficult in front. Vascularization was abnormal and intricate. At no point could any mass of calculous

6. Bailey, M. K., and Eberhart, C. A.: Large Renal Calculus, J. A. M. A. **111**:610-612 (Aug. 13) 1938.

7. von Illyés, G.: Ueber die Insuffizienz bei Steinniere, Ztschr. f. urol. Chir. u. Gynäk. **44**:63-73, 1938.

8. Chaton, M.: Extraction d'un calcul du bassinet par voie transpéritonéale dans un cas de rein en fer-a-cheval, J. d'urol. **45**:56-59 (Jan.) 1938.

consistency be palpated. In view of the difficulties involved in further exploration it seemed prudent to terminate the operation, closing the wound without drainage.

After some weeks of rest in bed all symptoms disappeared, and the patient was dismissed from the hospital. One year later the hematuria recurred. A roentgenogram again revealed a calculus of the pelvis of the right kidney. Owing to the difficulties encountered by the lumbar approach at the first operation, the kidney was exposed by the transperitoneal route. A horseshoe kidney, with isthmus at the lower poles, was revealed. Within the upper right portion of the organ, in what appeared to be the pelvis, was a sclerolipomatous mass the size of a hen's egg. Below this was a canal 3 cm. in length, resembling a ureter but leading into a second, abnormal pelvis on the same side. Incision of this lower pelvis revealed a stone the size of a walnut, which was removed. The sclerolipomatous tumor was not destroyed but was utilized to reenforce the suture. This tumorous mass, with well defined outlines, had developed from the center of irritation and chronic inflammation caused by the stone.

In operative intervention on a horseshoe kidney the extraperitoneal route of approach, recommended by Gutierrez, Papin and others, would seem to give the most satisfactory results. Occasionally, however, there are unusual circumstances in which a transperitoneal operation gives a better result.

Hydronephrosis.—Eichelberger [9] produced experimental hydronephrosis by increased intraureteral pressure resulting from partial constriction of the ureter. Experimental hydronephrosis has been classified into two goups: the chronic form, in which approximately 50 per cent of the renal tissue is destroyed, and the progressive form, in which the greater part of the renal tissue is destroyed. Chemical studies of the blood serum of animals with the chronic condition disclosed no significant deviation from the normal. In animals with the progressive condition the following significant changes were found in the uremic stage: marked acidosis; retention of nonprotein nitrogenous constituents, and increased concentrations of calcium and inorganic phosphorus, unaccompanied by any change in the total concentration of protein but accompanied by an increased albumin-globulin ratio.

Tumors.—Soloway [10] reported a series of 130 cases of renal tumor. In 90 cases the growth was discovered at operation and in 45 at necropsy.

9. Eichelberger, L.: Experimental Hydronephrosis in Dogs: I. The Composition of Blood Serum. J. Urol. 40:366-377 (Sept.) 1938.

10. Soloway, H. M.: Renal Tumors: A Review of One Hundred and Thirty Cases. J. Urol. 40:477-490 (Oct.) 1938.

Hypernephroid carcinoma is the most common type of renal neoplasm; it occurred in 91 cases (70 per cent). This type of tumor is characterized by its tendency to invade the renal vein and the vena cava, by its slow, progressive growth and relatively late symptoms and by its tendency to produce hematogenous metastasis. The metastatic growths are formed especially in the lungs and in the bone and often are the first clinical evidence of the disease.

Renal tumors occur more frequently among males than among females (96 to 34) and most often in the fifth and sixth decades of life (75 cases; 57 per cent). The ratio of white to Negro patients was about 8 to 1.

The classic triad of symptoms—hematuria, tumor and pain—occurred in about 20 per cent of cases. The appearance of all three symptoms in the same case nearly always occurred late in the course of the disease, after metastasis had taken place. Hematuria was found in 63 per cent of cases, tumor in 53 per cent and pain in 37 per cent.

Seventeen of the 40 patients who were not operated on did not have any urinary symptoms, and on repeated examination erythrocytes were not found in the urine. The condition of this group of patients was most difficult to diagnose.

Metastasis occurred in 93 per cent of the cases in which necropsy was performed and in about 15 per cent of the cases in which operation was performed.

Nephrectomy, as early and as radical as possible, is the operation of choice. In the presence of ureteral involvement the entire ureter, with a section of the bladder, should be removed. High voltage roentgen therapy should be employed preoperatively and postoperatively in all cases.

Tuberculosis.—Thomas, Stebbins and Petter [11] in discussing the diagnosis and indications for treatment of renal tuberculosis stated that urinalysis should be performed every three months in all cases of tuberculosis.

The destructive lesions of renal tuberculosis can be identified only by means of retrograde pyelograms taken after the pelvis has been well filled with an opaque substance.

As with another type of tuberculosis, there is an early, or "invasion," stage of renal tuberculosis. This period may be symptomless, but careful search will reveal clinical findings that are sufficient for diagnosis. The diagnosis and prompt treatment of the early lesion of renal tuberculosis may prevent the development of renal phthisis.

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11. Thomas, G. J.; Stebbins, T. L., and Petter, C. K.: The Diagnosis and Indications for Treatment of Renal Tuberculosis, Am. J. Surg. **38**:57-65 (Oct.) 1937.

Surgical treatment for any type of tuberculosis (except in an emergency) should not be undertaken until the patient has developed a sufficient defense mechanism. Surgical treatment of urogenital tuberculosis is rarely an emergency procedure. Surgical or medical treatment of tuberculosis should aim at the patient as a whole, not alone at the local lesion.

Renal tuberculous lesions or other urogenital lesions are local manifestations of a constitutional disease. Nondestructive renal tuberculosis, unilateral or bilateral, is a nonsurgical condition and should be treated intensively by medical methods. Bacilli of tuberculosis obtained in one specimen of urine from the renal pelvis do not constitute an indication for nephrectomy.

In cases of early renal tuberculosis, surgeons should be conservative in advising removal of a kidney which eliminates bacilli of tuberculosis unless the pyelogram reveals definite evidence of erosion and unless the urine from the second kidney repeatedly gives negative results when injected into animals.

Unilateral, slightly destructive tuberculosis should be treated conservatively under careful observation. Nephrectomy is indicated only when progressive disease is present. Extensive unilateral destructive lesions should be treated by surgical methods. In cases of bilateral destructive renal tuberculosis operation is not indicated except to stop hemorrhage or to relieve pain and sepsis due to an obstructed ureter.

Tuberculous patients should have careful preoperative treatment.

Heliotherapy is beneficial, but ultraviolet irradiation should be used only in selected instances.

Thomas, Kinsella, Petter and Stebbins[12] stated that the proper surgical treatment of renal tuberculosis is predicated on: (1) a thorough understanding of tuberculosis: where it begins, how it spreads and what measure of resistance the patient has against the bacillus of tuberculosis; (2) an understanding that it is rarely possible entirely to extirpate tuberculosis, so that surgical treatment for renal disease is not aimed at cure but is an aid in obtaining a clinical result; (3) the fact that in more than 50 per cent of all cases in which there are early or late lesions of renal tuberculosis the disease can be arrested in the kidney by medical methods only; (4) the fact that all patients who require surgical treatment for renal tuberculosis recover more quickly if medical treatment is instituted both before and after the surgical treatment than otherwise; (5) the fact that no operative mortality is necessary; (6) the fact that the only complication should be a post-

12. Thomas. G. J.; Kinsella, T. J.; Petter. C. K., and Stebbins, T. L.: Surgical Treatment of Urogenital Tuberculosis. J. Urol. **39**:766-783 (June) 1938.

operative sinal infection or late meningitis, and (7) the fact that if the proper methods of treatment are used ultimate arrest of the infection should occur in 90 per cent of cases.

Lieberthal [13] described the development of the tuberculous renal lesion from its earliest to its end stages by reconstruction of the clinical picture and of the gross and histologic changes in 270 cases of renal tuberculosis.

The tuberculous renal lesion is never primary but is hematogenous, occurring through the medium of embolism. The initial lesions are usually bilateral and because of the peculiarities of the renal circulation are usually cortical. They have a tendency to heal, but occasionally a tubercle will continue to grow. It then breaks into a tubule and discharges organisms, which infect the papilla, producing a papillary ulcer which is the key lesion of renal tuberculosis.

Until the development of the papillary ulcer the disease is latent and cannot be diagnosed clinically. As soon as the caseous papillary ulcer appears, however, there is open tuberculosis with descending infection of the urinary mucous membranes as well as ascending infection of the previously uninvolved portions of the renal tissue. Tuberculous strictures and urinary stasis resulting from the lesion in the mucous membrane play an important part in spread of the renal lesion. The papillary ulcer produces tubular obstruction and a tuberculous cavity which involves the pyramid through a combination of hydronephrotic change and tuberculous erosion.

As a result of the ureteral obstruction the tuberculous urine has a tendency to stagnate in the renal pelvis and to infect the previously uninvolved papilla. Erosion of small vessels with dissemination of tubercle bacilli through the portion of renal tissue supplied by the vessels is an important mode of progression of this type of renal lesion. This produces chains of tubercles extending radially from the eroded part to the surface of the kidney.

Then the original caseous erosion of each renal papilla progresses to formation of large cavities with thin-walled partitions of the columns of Bertini between each two cavities. The stagnant tuberculous urine becomes inspissated, forming the "putty" or "mortar" kidney.

The onset of a secondary infection produces the changes of pyelonephritis and eventually pyonephrosis, with extensive peripelvic and perirenal fibrolipomatosis. Occasionally there is a fulminating infection in which the lesion of the mucous membrane dominates the picture, producing caseous pyeloureteritis.

13. Lieberthal, F.: Renal Tuberculosis: The Development of the Renal Lesion, Surg., Gynec. & Obst. **67**:26-37 (July) 1938.

Although during the latent stage small, isolated tubercles may appear in the opposite kidney, these are not demonstrable clinically but are found at necropsy. It is said that renal tuberculosis usually is clinically unilateral and pathologically bilateral.

The opposite kidney may be, and usually is, finally involved by an ascending infection from involvement of the bladder and ureteral orifice, with consequent ureteral insufficiency and reflux of the tuberculous urine.

Emmett and Braasch [14] stated than an analysis of the methods of diagnosis employed in 100 consecutive cases of proved renal tuberculosis suggested that in more than two thirds of the cases the problem is not to establish the presence of the disease but to determine the degree of involvement of each kidney. Excretory urographic study is becoming more important in this field of diagnosis and is supplanting retrograde pyelographic examination in a large percentage of cases. However, retrograde pyelographic study is still of importance in differential diagnosis in a small group of cases in which the nature of the disease is in doubt and in an occasional case in which the lesion is exceedingly small and circumscribed.

As a result of excretory urographic study, repeated cystoscopic examinations should be entirely unnecessary; one examination will suffice in nearly all cases. A combination of excretory urographic examination with microscopic examination and staining of the specimen of urine obtained by catheterization of the ureter of the so-called good kidney is no doubt the best procedure to follow at present and supplies sufficiently accurate information in most cases to establish a satisfactory diagnosis and to permit the urologist to decide on the proper treatment.

The most common manifestations in the excretory urogram of the tuberculous kidney, in order of their frequency, are: (1) no visualization; (2) delayed visualization; (3) caliectasis; (4) evidence of necrosis in the outline of the calices; (5) cicatricial deformity of the calices and "pinching off" of the tips of minor calices or obliteration of the calices; (6) deformity or dilatation of the ureter, and (7) pyelectasis.

Jameson [15] studied the incidence of renal tuberculosis among patients with active pulmonary tuberculosis at Saranac Lake. The records of the Saranac Laboratory and of the Trudeau Sanatorium Laboratory

14. Emmett, J. L., and Braasch, W. F.: Has Excretory Urography Replaced Retrograde Pyelography in the Diagnosis of Renal Tuberculosis? J. Urol. 40:15-23 (July) 1938.

15. Jameson, E. M.: Renal Tuberculosis in Patients with Active Pulmonary Tuberculosis, Surg., Gynec. & Obst. 67:56-62 (July) 1938.

were examined to determine how often tubercle bacilli were present in the urine of patients who had pulmonary tuberculosis and whose urine contained other abnormal elements.

The criterion for examination at the Saranac Laboratory was an abnormal number of pus cells in a voided morning specimen of urine, and the criterion at the Trudeau Sanatorium Laboratory was albuminuria. In the latter laboratory, smears were made of sediment from a subsequently obtained twenty-four hour specimen.

It was shown that tubercle bacilli were found much more frequently in smears made from the sediment of the twenty-four hour specimen than from that of the single morning specimen. In only 1 instance was urine which gave a negative smear determined, by inoculation of guinea pigs, to contain tubercle bacilli. This was a twenty-four hour specimen.

In 88 cases of pulmonary tuberculosis in which acid-fast bacilli were found in smears of the sediment of voided urine, inoculation of guinea pigs proved the organisms to be tubercle bacilli (62.3 per cent of the males and 31.4 per cent of the females). Pyuria, albuminuria, erythrocytes and casts were reported to be present twice as frequently in urine containing tubercle bacilli as in urine containing nonpathogenic forms of acid-fast bacilli.

The necropsy records of 239 patients who died from active pulmonary tuberculosis were examined to determine the incidence of renal lesions. A total of 67, or 28.4 per cent (31 per cent of the males and 22 per cent of the females), had renal tuberculosis. In 20.9 per cent this was of the latent, or pathologic, type (nonprogressive, usually miliary), and in 7.1 per cent it was of the clinical, or open, type. The condition was bilateral in 76 per cent of cases of both types. Eighty-eight per cent of the patients with the clinical type of the condition were males. Thus, males not only had a greater tendency to renal tuberculosis than had females, but the patients who had clinical, or advanced, lesions were in the proportion of 3 males to 1 female.

Jameson [15] concluded that careful and repeated search for acid-fast bacilli should be made in smears of the sediment of a twenty-four hour specimen of urine of every tuberculous patient if pus or albumin is present in the urine. In such smears, properly stained, acid-fast organisms can be found in a high percentage of positive cases. In doubtful cases and in all cases in which acid-fast bacilli have been demonstrated, further examination should be made by inoculation of guinea pigs or by culture. Renal tuberculosis was three times as frequent among males with pulmonary tuberculosis as among females with pulmonary tuberculosis in the series of cases under consideration, and the lesions of 76 per cent of the patients were bilateral. Patients with renal tuber-

culosis rarely have "normal" urine, although the presence of tubercle bacilli in the urine depends on the existence of a lesion in communication with the pelvis of the kidney.

Trauma.—Priestley and Pilcher [16] reviewed the records of 45 patients whose kidneys had become ruptured. The majority were young men. Only those cases were considered in which the kidney was ruptured by external violence without penetration of the skin. The type of renal injury varied from slight subcapsular hemorrhage to complete pulpefaction of the kidney. In some cases the ureter or the renal pedicle was completely avulsed. Hemorrhage, usually perirenal but occasionally intraperitoneal, was uniformly present, and hematuria, either gross or microscopic, occurred in 95 per cent of the cases. Leakage of urine around the kidney was common. Serious associated injuries elsewhere in the body were present in 13.3 per cent of cases. Priestley and Pilcher found that healing may occur satisfactorily with medical treatment. On the other hand, urinary fistulas, hydronephrosis, pseudohydronephrosis, pyelonephritis or other anatomic abnormalities may persist or develop. Trauma, hemorrhage and pain are cardinal points to consider in the diagnosis, but they should be substantiated by intravenous urographic examination. In general, medical treatment immediately after the injury is preferred unless it is contraindicated by excessive hemorrhage or by the presence of a large perirenal mass. In certain cases in which patients are treated medically, subsequent operation may become necessary.

The 2 deaths that occurred in this series of 45 cases were attributed to severe extrarenal trauma. Thirty-one patients were followed for periods ranging from four to twenty-six years after injury. Eleven patients who underwent nephrectomy were entirely free of symptoms; 73.7 per cent of those treated medically were entirely well, and the remainder of this group had mild symptoms referable to the urinary tract.

Carbuncle.—Suter [17] discussed the literature on renal carbuncle and reported 5 cases from his own practice. He stated that surgical treatment should be as conservative as possible. In some cases it is impossible for the surgeon to avoid removing the kidney because the differential diagnosis between tumor and abscess cannot be made with certainty. In some cases the situation of the carbuncle makes removal of the kidney necessary.

16. Priestley, J. T., and Pilcher, F., Jr.: Traumatic Lesions of the Kidney. Am. J. Surg. **40**:357-364 (May) 1938.

17. Suter, F.: Diagnose und Therapie des Nierenkarbunkels, Schweiz. med. Wchnschr. **68**:634-636 (May) 1938.

URETER

Tumor.—Parker [18] pointed out that while many cases of malignant tumor of the ureters have been reported, benign tumors of this organ are relatively rare. He reported a case of papilloma in which the patient was an elderly man who came for observation after a painless hemorrhage of the ureter. A catheterized specimen from the left ureter was composed almost entirely of blood, and the ureter was found to be completely blocked 3 cm. above the bladder. According to the patient, several small stones had been passed two years previously. The left ureterogram revealed a large lacuna in a markedly dilated ureter, above which no opaque substance passed. By intravenous urographic examination the left kidney was shown to be larger than normal, with the lowermost calix compressed from below; observers saw the faint shadow of a cyst which appeared to be attached to the kidney and to be movable with it.

At operation the tumor of the ureter was found to hang like a pendulum by its pedicle at a point in the wall of the ureter above the bladder. Above this point the ureter was atrophied; below it, hypertrophied. Histologically its general structure was that of a papilloma derived from a cylindric epithelioma, formed of an arborescent, fibrous stroma covered with a thick layer of epithelioid cells. Most of the tumor was histologically benign, although at one point there appeared to be infiltration of the stroma by a small group of cells with rather hyperchromatic nuclei; this might suggest malignant transformation. It was possible that this was an oblique section made through the wall of the ureter, where the normal cells are brightly colored. Clinically nothing indicated a malignant tumor. The ureter was not adherent to the walls, and it was easily dissected free. The operative results were excellent, and at the time of Parker's report the patient had completely recovered.

An intensive study of the literature by Chauvin and Cerati revealed reports of 112 cases of tumor of the ureter, of which a third were benign; only 8.3 per cent of the patients gave histories of renal calculi. Most of the authors noted the classic sign of increased hematuria following ureteral catheterization. A significant factor noted in this case was the presence of a typical lacuna in the roentgenographic silhouette of the ureter after injection of an opaque substance. The shadow had the typical form of a champagne goblet. Shadows of this kind are not observed in cases in which multiple papillomas are metastatic from a renal tumor. Most of the other primary ureteral tumors mentioned in

18. Parker, G.: Un papillome primitif de l'uretère, J. d'urol. **45:**38-44 *(Jan.)* 1938.

the literature were adenopapillomas or malignant epithelial tumors. Tumors of mesodermal origin (leiomyomas and fibromas) are also found.

Stone.—Alyea[19] stated that the principles employed in cystoscopic removal of ureteral calculi are dilatation, lubrication and anesthetization of the ureter and dislocation, grasping or crushing of the calculus. The most widely used procedures are manipulation with catheters, bougies, spiral corkscrew stone dislodgers and cagelike instruments for grasping the calculus. The indications and contraindications for cystoscopic removal of ureteral calculi must be carefully considered before a decision is made.

Calculi may remain in the lower third of the ureter for several years without causing serious damage to the upper part of the tract. The calculi always have grooves in them or permit the urine to escape around them in some other way.

A series of 327 cases in which ureteral calculi were present were analyzed; in 72 per cent the calculi were removed cystoscopically.

A technic of catching the calculus with multiple twisted catheters was described. The idea of continued traction on the calculus by means of a simple apparatus was suggested.

The use of spinal anesthesia for ureteral relaxation at the time of extraction may be helpful.

Torsion.—Berry[20] reported a case of bilateral pelviureteral torsion associated with stenosis of the ureterovesical junctions and hydroureters; the patient was a boy 7 weeks of age. The condition was discovered at necropsy, and a cast was made of the urinary tract in order to present the features of the lesions as they appeared in vivo. A case of bilateral pelviureteral torsion has not heretofore been described in the literature.

Fistula.—Findlay[21] reported a case in which a ureterovaginal fistula was successfully repaired by combined vaginal and transvesical operation.

Ureterovaginal fistulas may be due to (1) congenital ectopic ureter, (2) obstetric injury or (3) surgical injury. A congenital ureteral opening into the vagina or vestibule cannot be regarded as a true fistula, since it is not acquired.

Obstetric injuries are not now common causes of ureterovaginal fistulas. Morris (1900) stated that the obstetric methods practiced in his time gave rise to numerous ureterovaginal and vesicovaginal fis-

19. Alyea, E. P.: Cystoscopic Removal of Large Ureteral Calculi. J. Urol. **40**: 83-100 (July) 1938.

20. Berry, J. V.: Bilateral Torsion of the Ureter: Case Report and Brief Review of the Literature, J. Urol. **40**:378-383 (Sept.) 1938.

21. Findlay, H. V.: A Uretero-Vaginal Fistula Successfully Repaired by Combined Vaginal and Transvesical Operation. J. Urol. **40**:384-389 (Sept.) 1938..

tulas. In the recent literature there are few reports of ureterovaginal fistula occurring in the practice of a qualified obstetrician, but in the presence of prolonged labor the same injury may occur.

The greatest number of ureterovaginal fistulas are directly attributable to some form of surgical accident. Because of his particular activity in this field the gynecologist is doubtless responsible for most of these injuries, which occur in the performance of either vaginal or abdominal pelvic operations.

Findlay reported the case of a woman aged 59 whose uterus was markedly prolapsed. Sixteen years previously she had undergone myomectomy and perineorrhaphy.

Vaginal hysterectomy was performed. This was followed by persistently flowing moisture in the vagina. Cystoscopic study revealed granulation tissue near the left ureteral orifice.

Vaginal examination through a defect in the vaginal fascia which easily admitted three fingers revealed a rather marked enterocele. This enterocele herniated about 2 inches (5 cm.) down into the vagina. The fistulous opening could be seen in the left vault of the vagina, at the end of the transverse scar of the vaginal hysterectomy, lateral to the enterocele. The fistula admitted a no. 6 ureteral catheter, which was passed easily to the renal pelvis, and a pyelogram was taken. The bladder was again filled with 400 cc. of methylene blue solution, but none appeared in the vagina; as a matter of fact, the fistula continued discharging clear, colorless urine.

Operation was performed in an effort to close the ureterovaginal fistula. At first another unsuccessful attempt was made to pass a catheter through the bladder and up the left ureter. Then a catheter was passed through the vaginal opening of the fistula up the ureter to the kidney, and after this was withdrawn another catheter was passed through the opening and into the bladder. It was hoped that if a catheter could be passed along the ureter from the bladder to the kidney, cystotomy could be avoided, but even a small catheter could not be passed in both directions through the fistulous opening. In view of this failure the fistulous tract was dissected through the vagina, and the vaginal mucous membrane and fascia were undercut so that the *edges* could be firmly approximated with a single row of black silk sutures rather deeply placed. Cystostomy was then performed, and a silver probe was passed up the left ureteral orifice, well beyond the ureteral stricture, which was just distal to the fistula. The probe was then lifted in order to elevate the bladder, and the intramural portion of the ureter was cut through with a cautery down to the silver probe. This cut was carried through the stricture back to the normal ureter. The bladder, muscle and skin were closed in layers around a Freyer tube, and a cigaret drain was placed in the space of Retzius.

The patient had an uneventful convalescence as far as her general condition was concerned. The ureteral catheter remained in place for sixteen days. The suprapubic tube was not removed until the twentieth day. A week after its removal the wound was completely healed, and the patient was up and about, with perfect control of urine.

<div align="center">BLADDER</div>

Anomaly.—Ignatescu, Slobozianu and Athanasiu-Vergu [22] reported 2 rare instances of agenesis of the bladder, with ureters opening into the uterus. The patients were twin sisters. The fetuses, stillborn in the seventh month, each presented an abdominal eventration. Such an anomaly is due to primary defective formation of the urinary apparatus. The fetuses belong in the class of celosomian monsters. The lower part of the body and the lower limbs were well developed. The presence of genitourinary organs and the existence of limbs place them also in the class of aspalasomas. The malformations, which were multiple, were almost identical in the two fetuses. Each had lumbar spina bifida with myelomeningocele; in both the large intestine and the gallbladder were lacking. In 1 fetus both ureters and in the other a solitary ureter from a solitary kidney debouched into a well developed uterus, which, however, lacked a cervix. Each had one hydronephrotic kidney. In 1 fetus the other kidney was normal. In the other fetus the small intestine occupied the site of an agenetic kidney. The ureters were long, sinuous and distended.

The absence of a bladder has been observed by the authors in symmelians and in infants with a persistent cloaca.

The aplasia of the anterior region which gave rise to eventration and at the same time to anomalies of the urinary apparatus must be of the same nature as that of the posterior region, where it caused spina bifida. The anomaly in monsters of celosomian type consists in defective development of the somatopleures, which allows the abdominal organs to herniate.

Tumor.—Adams reported a case of endometriosis of the bladder. He stated that this condition frequently is confused with other vesical lesions, particularly with malignant tumor. The occurrence of an intramural tumor of the bladder, presenting a bluish, cystic appearance on its surface, frequently resembling a varix, in a case in which there is a history of periodic attacks of pain, frequency, hematuria and dysuria occurring in the course of menstruation is typical of endometriosis of the bladder.

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22. Ignatescu, M.; Slobozianu, H., and Athanasiu-Vergu, E.: Absence de la vessie et abouchement des uretères dans l'utérus chez deux jumelles, J. d'urol. **45**: 51-55 (Jan.) 1938.

Adams [23] reported the case of a woman 36 years of age. Salpingo-oophrectomy was performed on the right. At the same time a number of adhesions between the uterus and the bladder were noted. Several weeks after the operation the patient had severe dysuria. At that time cystoscopic examination disclosed an intramural tumor. Pelvic examination revealed a tumor in the region of the fundus of the bladder. Suprapubic cystotomy was performed, and a tumor of the bladder was found. The tumor was about 3 cm. thick and was free of pericystic involvement. The tumor was resected and the bladder closed. At a later examination it appeared that the patient was cured.

The symptoms of vesical endometriosis depend on the extent and situation of involvement of the bladder and also on the presence or absence of involvement of other pelvic organs; that is, on whether the vesical involvement is primary or secondary. The symptoms consist of frequency of urination, dysuria and hematuria, which appear several days before menstruation, persist during the flow and generally continue for a day or two after its cessation. Hematuria is seldom macroscopic and is present only during the menstrual periods. The symptoms are insidious in onset and show a progressive increase in severity. Usually a tumor is palpable on pelvic examination. If the tumor is secondary there will be other symptoms. The most prominent is acquired, progressive dysmenorrhea affecting a patient who is more than 30 years of age and who has no history of infection. There are usually definite but not characteristic abnormalities in the menstrual flow. The pelvic findings in well marked cases are similar to those of chronic pelvic inflammation.

The symptomatic triad frequency, dysuria, and hematuria occurring cyclically with menstruation, together with the presence of a pelvic mass, is suggestive of primary endometriosis of the bladder.

The cystoscopic findings are diagnostic in most cases if the examiner will keep in mind the possibility of endometriosis. The tumor usually involves the fundus, is about 2 to 4 cm. in diameter, is well circumscribed and is slightly or moderately elevated from the vesical wall, depending on the amount of vesical distention. The mucous membrane of the bladder is intact over the surface of the tumor, and the tumor itself is rather soft. The tumors are single and seldom undergo ulceration.

Treatment is variable and depends on many factors. As bilateral oophorectomy or irradiation of the ovaries removes the hormonal stimulation necessary for continued growth of a heterotopic endometrioma, artificial menopause would seem indicated if the patient is at or near the menopause or if involvement of the bladder is too advanced for

23. Adams, P. S.: Endometriosis of the Bladder: Report of a Case, J. Urol. 40:390-396 (Sept.) 1938.

successful complete removal of the growth. For the primary type of tumor, excision of the vesical lesion is the method of choice in treatment of young women who are desirous of having children. Even for the secondary types of endometriosis of the bladder excision may be done, with a good chance of nonrecurrence.

Kirwin [24] stressed the necessity for careful study of the size, situation, histologic structure and stage of advancement of vesical tumors as a basis for selection of proper treatment. Three distinct types of treatment are employed, either separately or in combination: operation, diathermy and irradiation.

Only 23.4 per cent of vesical tumors are so situated that they can be removed by segmental resection of the bladder. Despite the increase in the number of cases in which total cystectomy is performed for carinoma, Kirwin said that any operation involving ureteral implantation is unjustified if the patient is elderly or enfeebled and that at best the outcome of such a procedure is highly uncertain.

Although diathermy is employed routinely in treatment of benign growths, it never has been satisfactory when used alone in treatment of malignant growths. Radium and roentgen therapy, although valuable adjuncts to other methods, are also unsatisfactory when used alone. No one method can be adapted to all cases.

Kirwin outlined various combinations of all three methods which will fulfil the requirements of conservative practice in the great majority of instances. They are listed as: (1) resection using clamps; excision by scalpel, followed by high voltage roentgen therapy; (2) resection by cautery knife, with implantation of radon seeds before the wound is closed; (3) fulguration by loop and disk electrodes through a suprapubic incision, followed by implantation of radon seeds, and (4) a closed method (removal of the exuberant portion of the growth by the resectoscope, followed by intraurethral implanation of radon seeds and in some cases by external roentgen therapy).

Diverticulum.—Ward [25] reported 53 cases of vesical diverticulum. The average age of the patients was 57 years: the youngest patient was 15, the next older 18 and the next 32; 10 were in the forties. and the oldest was 80. All were males except 1. who suffered from urethral stricture and whose diverticulum was not yet large enough to require resection. In only 2 cases could the diverticulum be considered of congenital origin; in 1 of these the patient was a boy aged 15 years.

24. Kirwin, T. J.: The Management of Bladder Tumors, Surg., Gynec. & Obst. **66**:999-1007 (June) 1938.
25. Ward, R. O.: Fifty-Three Cases of Vesical Diverticula, Brit. J. Surg. **25**:790-815 (April) 1938.

A vesical diverticulum does not give rise to any unique symptoms, and only rarely can its presence be detected on general physical examination. The patient is commonly unaware that anything is wrong with him unless the urine becomes infected or until increasing difficulty or frequency of micturition arouses his interest.

Frequency of micturition is the commonest symptom and is not due so much to the diverticulum itself as to associated cystitis or prostatic enlargement. Pain on micturition is the next most usual symptom and is also commonly due only to cystitis. In this series infection was present in all but 2 cases. Difficulty of micturition undoubtedly is the most characteristic symptom. Thirty-six patients suffered from it, and of this number 14 either had retention of urine or had suffered from it intermittently. Such difficulty is not necessarily due to the presence of a diverticulum, for in 30 of these cases prostatic obstruction also was present.

In this series of 53 cases diverticulectomy alone was performed in 15 instances; diverticulectomy combined with treatment of prostatic obstruction, either by prostatectomy or periurethral resection, in 21 instances, making a total of 36 cases in which diverticulectomy was performed. There was 1 death immediately after diverticulectomy. One patient died after the second stage of prostatectomy. Two patients died after cystostomy. One, who had multiple small diverticula that had not been subjected to treatment, died because one of these diverticula was ruptured when a Bigelow evacuator was being used after a vesical calculus had been crushed. Litholapaxy never is employed when diverticula are of large or moderate size, because of the obvious impossibility of recovering the fragments of the calculus. This case is included in order to show that in the presence of even small pouches litholapaxy carries a risk which is not well recognized. One patient died three months after diverticulectomy and prostatectomy; 1, three weeks after periurethral resection of the prostate gland; 1, twenty months after diverticulectomy; 1, four and one-half years after diverticulectomy and prostatectomy (of apoplexy), and 1, twelve years after the operation, of another disease. The other patients, as far as can be ascertained, are alive and well.

Paralysis.—Ferguson and Watkins [26] discussed paralysis of the bladder and associated neurologic sequelae of spinal anesthesia (cauda equina syndrome).

From time to time there have appeared in the literature reports of cases in which neurologic complications—varying from headache, menin-

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26. Ferguson, F. R., and Watkins, K. H.: Paralysis of the Bladder and Associated Neurological Sequelae of Spinal Anaesthesia (Cauda Equina Syndrome), Brit. J. Surg. **25**:735-752 (April) 1938.

gism, cranial nerve paralysis and focal cerebral lesions to radiculo-myelitis and lesions of the cauda equina and the peripheral nerves—have occurred immediately or remotely after administration of a spinal anesthetic agent.

The authors recorded 14 cases in which a cauda equina syndrome developed after administration of a spinal anesthetic agent. Thirteen of these cases were observed within twenty months. Only 16 examples of this lesion were found in examination of the literature published before this period.

In the cases recorded by Ferguson and Watkins, almost immediately after the spinal anesthesia the following manifestations occurred: retention of urine, succeeded by incontinence; incontinence of feces with loss of anal sphincteric tone; impairment of sensation in the "saddle" area and in some cases also down the back of one thigh, and absence or diminution of one ankle reflex (occasionally absence of both ankle reflexes and even of the knee reflexes). It was clear from examination of all these patients that the basic lesion was the same but that the variations were due to different degrees of the same syndrome.

The vesical symptoms nearly always appeared within twenty-four hours of the operation, whereas rectal symptoms sometimes were delayed—in 1 case for ten days—almost suggesting a progressive lesion. Complete urinary retention developed after operation in all except 1 case, that of a female whose only apparent vesical disturbance was incontinence on one occasion. The period of complete retention varied from about a week to a month and was followed by incontinence of urine. Incontinence usually was of short duration (a few weeks) but in 2 cases was still present after more than two years. In the early stages of spontaneous urination there was always marked frequency of voiding. In 1 case this subsided in about 6 weeks; in 2 it passed off in six months. and in 4 others it was still troublesome for periods varying from nine to twenty-seven months after operation. Residual urine persisted for from six to twelve months or more and in 1 case was still present after twenty-seven months.

A sensation of numbness—at first constant and after about a year intermittent—in the saddle area was a universal complaint. This numbness was still present in some cases three years after the operation.

It is evident that the lesion under discussion is the direct result of administration of the spinal anesthetic agent. since in all cases it appeared immediately after operation. The clinical manifestations of the lesion might be explained either by damage to the lumbosacral portion of the cord or to the conus medullaris on the one hand. or to the nerves of the cauda equina on the other. For several reasons. however. it seems more probable that the maximal damage is to the latter.

Of the 14 cases in this series, the difficulty in 13 definitely followed employment of a heavy solution of the drug known as "duracaine" (a pseudohypobaric solution of procaine hydrochloride). It is probable, but not certain, that this drug also was utilized in the remaining case. Thirteen of these cases were observed in the Royal Infirmary in Manchester, England, 12 within a period of twenty months. During this period, about 1,000 instances of spinal anesthesia induced with "heavy" durocaine were reported in the hospital records. In addition, the records for this period include 650 instances of spinal anesthesia in which the drug is not named and 60 cases in which a light solution of durocaine was employed. The total number of cases in which durocaine was the anesthetic agent must, therefore, be between 1,000 and 1,700, giving a rate of incidence for this lesion of between 1 in 90 and 1 in 155 (if the doubtful case is included).

During the period from July 1933 to December 1935, stovaine (benzoyldimethylaminomethylpropanol hydrochloride) was administered at the Manchester Royal Infirmary 1,000 times and nupercaine 300 times (in addition to cases in which the anesthetic used was not mentioned). No case of paralysis was observed in this group.

Rupture.—Gaston [27] stated that trauma, not infrequently associated with alcoholism, is the commonest etiologic agent encountered in cases of intraperitoneal rupture of the bladder.

The laceration of the vesical wall usually runs in an anteroposterior direction across the dome of the bladder. Because of the obstacles to exposure, adequate closure of the posterior extremity of the laceration often is difficult.

A discussion of the special test whereby the diagnosis of intraperitoneal rupture of the bladder can be definitely established was presented.

Treatment of intraperitoneal rupture of the bladder is purely surgical and should encompass three aims: (*a*) treatment of the laceration of the vesical wall, (*b*) treatment of the peritoneum and (*c*) establishment of adequate drainage of vesical urine. A discussion of these factors and their relative importance was presented.

The mortality is directly proportional to the time which elapses between rupture and institution of adequate surgical treatment.

Wyatt and Douglass [28] reviewed the literature and presented 31 cases of spontaneous rupture of the tuberculous urinary bladder. In

27. Gaston, E. A.: Intraperitoneal Rupture of the Urinary Bladder, New England J. Med. **218**:958-963 (June 9) 1938.

28. Wyatt, T. E., and Douglass, H. L.: Spontaneous Rupture of the Tuberculous Bladder, J. Urol. **40**:506-512 (Oct.) 1938.

all cases of intraperitoneal rupture death occurred in spite of surgical intervention. Attempts at repair of 4 vesicovaginal fistulas of tuberculous origin failed.

The authors reported a case of spontaneous tuberculous vesicovaginal fistula of three months' duration. After nephrectomy and subsequent irrigations of the bladder with a weak solution of phenol the fistula healed almost spontaneously.

They concluded that spontaneous rupture of the tuberculous bladder is rare. Intraperitoneal rupture is more common than extraperitoneal fistula. Nephrectomy in the presence of unilateral renal tuberculosis, nephrostomy and ureteral transplantation are the only means of treatment. In the authors' opinion the prognosis of tuberculosis of the urinary tract depends more on the severity of the cystitis than on the degree of nephritis. After operation the cystitis must be controlled before the patient can recover.

Hernia.—Gayet and Cavailher [29] reported an unusual case of right inguinal hernia of the ureter and bladder. The patient, a very obese man aged 68, for many years had had an enormous, irreducible hernia in the right groin, which in the course of years had reached the size of the head of an adult human being. For several years he had suffered with attacks of hematuria and dysuria and had observed that often he could accomplish a difficult urination by making pressure on the hernia. An attack of complete retention of urine brought him under the authors' observation.

Catheterization proved impossible, the catheter stopping at the neck of the bladder. In the belief that a large part of the bladder, if not the entire organ, was in the abdomen, cystostomy was performed very low, behind the symphysis pubis. This elicited only a little gravel and a few drops of urine. The patient died on the following day.

At necropsy an enormous thick-walled sac was observed descending to the base of the scrotum; this proved to be the bladder itself, a flabby ovoid pocket containing but little urine. At the level of the very wide internal inguinal ring it became reduced to a sort of isthmus which continued into the abdomen for 3 to 4 cm., where it became prolonged into the urethra. It was completely inverted, so that the cystostomy wound, supposedly made in the anterior surface, was seen to be on the prolapsed posterior surface. Behind the bladder was observed the greatly dilated ureter, which was at first mistaken for an intestinal loop; most of it (15 to 20 cm.) was in the sac, which contained no intestinal loops. The right kidney was low, at the level of the crest of the ilium; at its

29. Gayet, G., and Cavailher: Hernie inguinale droite de l'uretère et de la vessie, J. d'urol. 45:193-198 (March) 1938.

superior pole there was a small bluish subcapsular cyst; the calices, the pelvis and the upper portion of the ureter were greatly distended. The left kidney was small and atrophic; the left ureter was normal.

Had it been possible to guess during life that the hernia consisted solely of the bladder and the greater portion of the ureter, it would have been simpler to make a puncture or a small incision that would have revealed the bladder within the scrotum and thus to establish a temporary opening to drain it. In the absence of this knowledge, however, the risk of finding the intestinal peritoneum within the hernia was too great. Even if a correct diagnosis could have been reached, reduction of such a hernia, reintegration of the ureter and closure of the hernial orifice constituted too long and laborious a procedure to be borne by a patient who was desperately ill and whose renal function was so defective.

Stone.—Wildbolz and Kohlschütter [30] stated that careful observation concerning spontaneous disintegration of vesical stones in man may perhaps lead to better treatment for stone in the urogenital tract. If the physician succeeds in most cases in determining the causes of spontaneous disintegration of stones, he may be able to fulfil the desire of patients and of physicians to remove even large stones without operative procedure.

Most stones which undergo spontaneous destruction are pure urate stones (75 per cent), associated with infected urine, and most of them are vesical stones; rarely are they renal stones.

Wildbolz and Kohlschütter gave an accurate review of their examination of pure urate stones which had undergone spontaneous disintegration. They concluded that the structure of the stone is chiefly responsible for the possibility of its disintegration and that the structure depends on the manner of its formation.

Reconstruction.—Friedrich [31] discussed the procedure of forming a new bladder from the intestine. In 4 cases of shrunken, contracted bladder he anastomosed a ring of small intestine and the bladder proper. He encountered no unusual operative difficulties. In 2 cases the results were excellent, and urination became normal. In the other 2 cases, although the capacity of the bladder increased to normal, there was no relief of symptoms referable to the urinary tract. He stated that this was probably due to the fact that the anastomosis was not sufficiently extensive and was too high at the vertex of the bladder, causing the intestine to act as a diverticulum.

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30. Wildbolz, H., and Kohlschütter, V.: Ueber Selbstzertrümmerung der Blasensteine, Schweiz. med. Wchnschr. **68**:872-875 (July) 1938.

31. Friedrich, H.: Ueber die Scheelesche Blasen-Dünndarmringplastik, Ztschr. f. Urol. **32**:420-424, 1938.

De Gironcoli [32] stated that many operations are required for the formation of a functioning intestinal bladder. Each operation carries a considerable risk, endangering the life of the patient without giving him relief from his symptoms or removing the diseased tissue. Even in cases in which an intestinal bladder is successfully formed there is no certainty that the patient will not have a descending infection of the urinary tract.

Incontinence.—Davies [33] stated that urinary stress incontinence, a disease peculiar to women, is caused by a disturbance of the urethral sphincters which makes them unable to retain urine when intra-abdominal pressure is increased. The condition may be caused by injury during labor to the bridge of musculofascial tissue between each two of the three openings of the pelvic outlet, the urethra, the vagina and the rectum; or it may be the result of general physical under-development in women who are unable to cause the muscles of the abdominal wall to contract or who are unconscious of a voluntary sphincter of the rectum or vagina. They cannot exert sufficient pressure against the urethral canal to withstand increased abdominal pressure and prevent leaking.

Davies gave a new conception of the urethral sphincter of the female. The urethra is composed of two layers of involuntary muscle fibers and at its origin from the bladder is encircled by an additional hyper-trophied layer of involuntary muscular fibers called the "internal sphincter." This mechanism is sufficient to retain urine in the bladder under ordinary circumstances. In addition, the action of the three muscular planes through which the urethra passes constitutes a voluntary sphincter which protects against leakage of urine when there is increased intra-abdominal pressure, such as occurs in laughing, coughing, aggressive intercourse or a fall.

The first muscular layer perforated by the urethra is the levator ani muscle, which, in the usual textbook descriptions, is represented as simply running lateral to it. As a matter of fact, fibers are supplied to the urethra and at times surround it for its entire length. When the levator ani muscle is contracted, the portion surrounding the urethra causes the urethra to undergo angulation anteriorly. The middle layer is the deep transverse perineal muscle which bridges the area bounded by the pubic arch, between the layers of the urogenital diaphragm.

32. de Gironcoli, F.: Eine Kritik zur künstlichen Harnblase, Ztschr. f. Urol. **32**:416-419 (June) 1938.

33. Davies, J. W.: Urinary Stress Incontinence: The Anatomical Defect Found and a Rational Method for Its Treatment. Surg., Gynec. & Obst. **67**:273-280 (Sept.) 1938.

This permits voluntary constriction of the urethra in its middle. The third layer is composed of the bulbocavernosus and the ischiocavernosus muscle, which lie lateral to the urethra but communicate anterior to it. They are not usually considered to be sphincters of the urethra, but their voluntary contraction results in posterior angulation of the distal portion of the urethra, just the opposite to the angulation produced by the levator ani at the proximal portion. This mechanism of voluntary sphincters acts as a protection against leakage by double angulation of the urethra and constriction of its middle.

Injuries to these sphincters during labor may result from tears or from ischemia. Treatment for urinary stress incontinence not caused by childbirth consists in development of the muscles through calisthenics and exercises of the levator as a whole. Attempts should be made to interrupt the urinary stream, and the vaginal sphincter should be intermittently contracted during intercourse. Venous stasis accompanying the condition is improved by assumption of the knee-chest position.

In cases in which there is anatomic damage, accurate reconstruction can be accomplished by first approximating the lacerated tissue of the base of the bladder. This repair when continued distally will result in reconstruction of the involuntary sphincter at the neck of the bladder and eventually of the levator ani muscle and the deep transverse perineal muscles. The superficial sphincter is reconstructed as the posterior perineal body is repaired. Of 50 patients with stress incontinence, 45 were cured by surgical treatment.

Purpura.—Meyer [34] described the clinical picture of purpura of the bladder and nonspecific ulcers of the bladder, surveying the literature and analyzing his own cases.

He had 23 patients with purpura and 52 patients with nonspecific ulcers of the bladder. In many instances it was found that the diseased condition of the bladder resulted from a focus of infection elsewhere. The vesical condition usually was improved by removal of these foci, even without local treatment, and even in cases in which most types of local treatment had been resisted healing could be brought about by eradication of the infection.

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34. Meyer, E.: Zur Frage der hämatogenen Entstehung von Blasenpurpura und unspezifischem Blasengeschwür, Ztschr. f. Urol. **32**:*369-392,* 1938.

(To be concluded)

CONGENITAL CYSTIC DILATATION OF THE BILE AND PANCREATIC DUCTS

NECROPSY THIRTEEN YEARS AFTER HEPATICODUODENOSTOMY

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CHICAGO

The case here described was previously reported [1] after relief of biliary obstruction by operation for congenital cystic dilatation of the common bile duct.

Later, diabetes developed, and finally hypertension with nephrosclerosis led to death. Necropsy showed cystic dilatation of the bile ducts and both pancreatic ducts, with many obstructive cysts in the latter and a hepaticoduodenostomy opening which had functioned normally for over thirteen years.

Congenital cystic dilatation of the common bile duct is characterized clinically by symptoms of intermittent or chronic obstruction. The onset usually occurs in infancy or early youth, with intermittent attacks of acute abdominal pain. It is usually followed by jaundice and by a palpable mass in the right upper quadrant of the abdomen.

Pathologically there is cystic dilatation of the common duct with evidence of a noninflammatory stricture or atresia near the outlet. Similar changes may involve the entire biliary duct system and both pancreatic ducts, as in the case to be reported.

REPORT OF A CASE

Mrs. S., aged 49 years and 10 months, was admitted to the Presbyterian Hospital on Nov. 6, 1922. She complained of attacks of colicky pain in the upper part of the abdomen. Such pain, with nausea or vomiting, had followed ingestion

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† Dr. McWhorter died Oct. 16, 1938.

1. McWhorter, G. L.: (a) Congenital Cystic Dilatation of the Common Bile Duct, Arch. Surg. 8:604 (March) 1924; (b) Preventive Surgery of the Pancreas and Bile Ducts, Illinois M. J. 47:128 (Feb.) 1925; (c) Results of Reconstruction of the Common Bile Duct: A Case Eight Years After Hepatico-Duodenostomy for Congenital Dilatation of the Common Bile Duct; Recent Diabetes Mellitus, S. Clin. North America 12:159 (Feb.) 1932.

of food for practically all of her life. The severe attacks were often followed by jaundice, which at times persisted for years.

According to her mother, these acute attacks of pain were first noticed at the age of 6 months and continued to occur in association with jaundice until the patient was 7 years old. During the attacks she often lay doubled up with her face down, and since the pains became worse on sitting she rarely attended school. She was a thin and delicate child and was never able to run and play.

From the age of 7 until her first pregnancy, at 19, the attacks of pain were less severe, but even then she was able to eat only small amounts at a time.

During her pregnancies the attacks of pain were worse after the fourth month, and they became more severe after the birth of her seventh child, eleven years previous to her admission to the hospital.

The menses had become irregular four years previously; none had occurred during the last year. Since then the attacks of pain had been worse and had occurred about every three or four weeks.

The acute pains started in the epigastrium. They occurred usually after meals, but sometimes they began at other times when the patient was working. They extended to the right upper quadrant of the abdomen and frequently radiated to the lower angle of the right scapula. They were sometimes followed by vomiting or chills, which in turn were followed by perspiration, but when the colicky pain stopped the patient would usually feel well.

A hypodermic injection had been necessary for relief of pain three or four times a year during the last fifteen years and more frequently during the last year. Because eating usually brought on pain or distress she frequently took only a cup of tea and a piece of bread.

There had been no other illness, and she had not had any children's disease. There was no history of a similar condition in her family. She had three brothers, four sisters and seven healthy children.

Fourteen years previously she had been operated on elsewhere, and drainage of the gallbladder had been done. Immediately after the bile stopped draining, however, the attacks recurred.

Physical examination showed a white woman of small stature, deeply bronzed from long-existing jaundice. Her weight was 95 pounds (43.2 Kg.), which was normal.

The abdominal wall was relaxed except in the right upper quadrant, where there was a palpable subcostal mass which could not be definitely outlined owing to moderate tenderness and rigidity. Otherwise the findings were normal.

The blood pressure was 178 systolic and 110 diastolic, but five days previously, during an attack, it had been 132 systolic and 60 diastolic, with a pulse rate of 72.

Examination of the gastric contents after an Ewald meal showed normal findings.

Roentgenograms of the urinary tract and the gallbladder region showed no abnormality except for several small dense calcified areas near the spine, which were thought to be in the pancreas.

A clinical diagnosis of obstruction of the common bile duct, probably due to calculi, was made.

Operation was performed on November 7. A large cystic dilatation of the common bile duct was found, which extended behind the duodenum and was connected to it by one short, friable, narrow-strictured segment of duct, which was not surrounded by pancreatic tissue. This tore off from the sac when it was freed. It was left attached to the duodenal wall, but it was so small that no lumen could be found by probing.

The gallbladder was small, with a thick, muscular wall. It was attached near the upper end of the dilated common duct. There were a few small, black, uniformly round calculi in the common duct, but there were none in the gallbladder. When the dilated intrahepatic ducts were explored, similar calculi weighing about half an ounce (15 Gm.) were removed.

The head of the pancreas was in normal relation to the duodenum. It felt firm and sclerotic, and several hard areas could be palpated.

The cystic common duct together with the gallbladder was removed, and the end of the dilated hepatic duct was anastomosed directly to the duodenum, which was sutured to the round ligament to relieve tension. Two cigaret drains were inserted.

Pathologic examination showed that the excised large cyst was formed by the dilated common bile duct, which joined the cystic duct and the hepatic duct at the upper end. The muscles of the gallbladder wall were hypertrophied, and there was normal epithelium in some areas, while other portions showed desquamation.

The wall of the dilated common duct consisted of fibrous tissue, with no muscle. The epithelium was absent, but there was no evidence of inflammation, which indicated that the desquamation had occurred during preparation of the section.

There was ½ ounce (15 cc.) of small, shotlike black pigment stones which were not opaque to the roentgen ray.

A fragment of liver attached to the gallbladder showed a moderate amount of congestion with many round and a few polymorphonuclear cells but no evidence of suppuration or cirrhosis.

Convalescence was uneventful except for a duodenal fistula which developed on the twelfth day and healed in two weeks. After the operation the patient was able to eat regular meals without distress or pain for the first time in her life.

One year later she had gained 20 pounds (9 Kg.) in weight and had no complaints, although she had been doing all of her own housework.

Fluoroscopic examination of the stomach was made, and roentgenograms were taken after ingestion of a barium sulfate meal at twenty-five days, at one year and at seven days after operation. All showed dilatation of the intrahepatic bile ducts, especially of one to the left lobe, but there was no evidence of stenosis at the hepaticoduodenostomy stoma (figs. 1 and 2). Roentgenograms taken twenty-four hours after ingestion of the barium meal revealed only traces of barium remaining in the intrahepatic bile ducts.

In May 1930, seven and one-half years after the operation, the patient reentered the hospital, suffering from severe diabetes with loss of weight and appetite. There was no complaint of her old attacks of pain or jaundice. At times, when bending over at housework after meals, she would have some distress and tenderness in the upper part of the abdomen, but it may have been partly due to constipation. The icterus index of the blood was normal. The blood pressure was 190 systolic and 80 diastolic.

A strict diabetic routine was prescribed, which required the continued use of insulin. The patient continued to do her housework except during a severe attack of bilateral lumbosacral neuritis which developed seven months later and persisted for several weeks.

In May 1935, about nine months before her death, she reentered the hospital, complaining of feeling sleepy during the daytime. She was given a stricter diabetic diet, with larger doses of insulin. The urine showed a moderate amount of albumin. She felt better after this and continued to do her own housework. There was some gain of weight.

In October she reported having gained some weight but had no complaints except for trouble with her vision.

About December 26 she became too weak to do her housework and remained in bed most of the time. Her appetite was poor, and she became restless.

Examination on Jan. 7, 1936, revealed physical weakness. There was enlargement of the heart to the left, with a marked systolic murmur and an occasional extra systolic beat. The blood pressure was 260 systolic and 140 diastolic. The pulse rate was 96. Since leaving the hospital she had completely lost vision in the right eye and could just see fingers with her left; this condition was due to cataracts. There was no tenderness or palpable enlargement of the liver, and other physical findings were essentially normal. The urine was alkaline, had a specific gravity of 1.012 and contained a large amount of albumin. There was a large amount of sugar, in spite of the use of insulin and a greatly restricted diet.
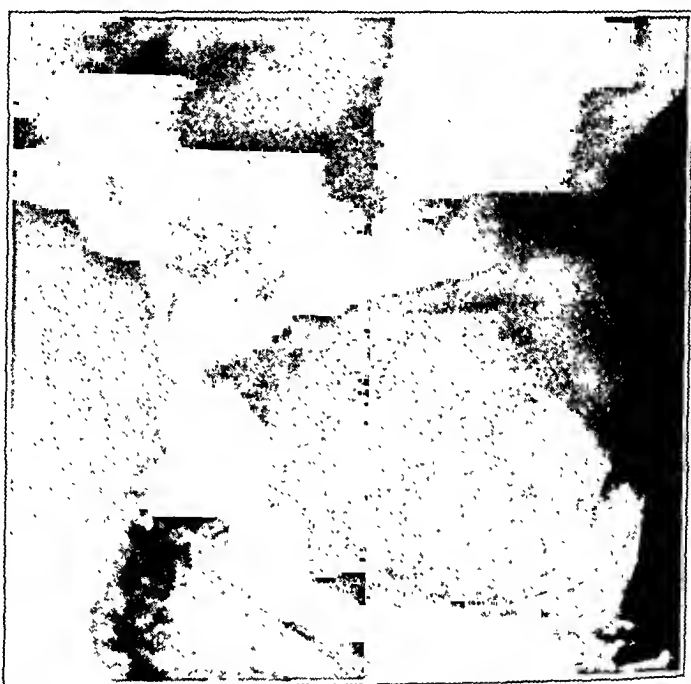
Fig. 1.—Branches of the dilated hepatic bile ducts after postoperative ingestion of a barium meal.

The patient gradually became weaker and died with symptoms of uremia on February 2, at the age of 63 years, over thirteen years after permanent relief of biliary obstruction by a hepaticoduodenostomy.

Necropsy was limited to the abdomen. The cadaver had been previously embalmed.

There were many adhesions beneath the operative scar. The liver weighed 1,075 Gm. and was normal in position, shape and size, but it was densely adherent to the duodenum at the site of the hepaticoduodenostomy. The gallbladder had been previously removed.

The head of the pancreatic mass appeared normal in size and shape, but it felt sclerotic, and the calculi could be palpated as several hard nodules. One large and several small cysts were observed involving the greater part of the pancreas. After evacuation of the cystic contents the pancreatic mass weighed 90 Gm.

The adrenal glands were both definitely enlarged. The kidneys appeared slightly smaller than normal, and the surfaces made by section showed narrowing of the cortex.

When the duodenum was opened the anastomosis to the hepatic duct, made in 1922, was observed 8 cm. from the pylorus. There was no narrowing of the opening, which was 1.1 cm. in diameter and was the same size as that part of the hepatic duct (fig. 3).

Proximal to the stoma was a redundant fold of the duodenal mucous membrane, which might have diverted some of the duodenal contents from the hepatic duct.

There were two dilated duct branches to the right lobe of the liver, which measured 8 cm. in length and 1.8 cm. in diameter. There were two large branches

Fig. 2.—Barium after rapid passage into the peripheral bile ducts. The largest cystic dilatation occurred in a branch to the left lobe. After twenty-four hours only traces of barium remained in the ducts. Roentgenograms taken one month, one year and seven years after operation showed the same conditions.

to the left lobe. The largest measured 3.5 cm. in diameter and 8 cm. in length. It ended beneath a fibrous wall 2.5 cm. across, which appeared on the upper surface of the left lobe. The lower second branch was 7 cm. long, with a diameter of 1.3 cm., and gave off a branch almost as large. All of the large ducts gave off small peripheral branches which were moderately dilated. The dilated main bile ducts were sacculated and cystic in shape, with noticeable narrowing at their junction with other ducts, but there were no true cysts in the liver.

The minor pancreatic duct entered the duodenum 10 cm. from the pylorus, opposite the hepaticoduodenostomy stoma. The papilla was closed in a normal

manner but admitted a probe 2 mm. in diameter, and the duct passed through the wall for a distance of 1 cm. The duct was normal, smooth and regular until it reached a point 1 cm. outside the duodenum, when the lumen became irregular and sacculated, with incomplete narrowing at intervals. There were two main irregularly dilated branches of minor duct extending into the pancreatic mass, which contained seven rough, irregular calcareous calculi opaque to the roentgen rays. There were also several small fragments. The largest measured 1 by 0.5 cm. and was S shaped to conform to the shape of the dilated duct. There were a number of smaller branches ending in dilated pockets, while one small, irregularly stenosed duct approximated a branch from the major duct about 2 cm. from the major papilla.
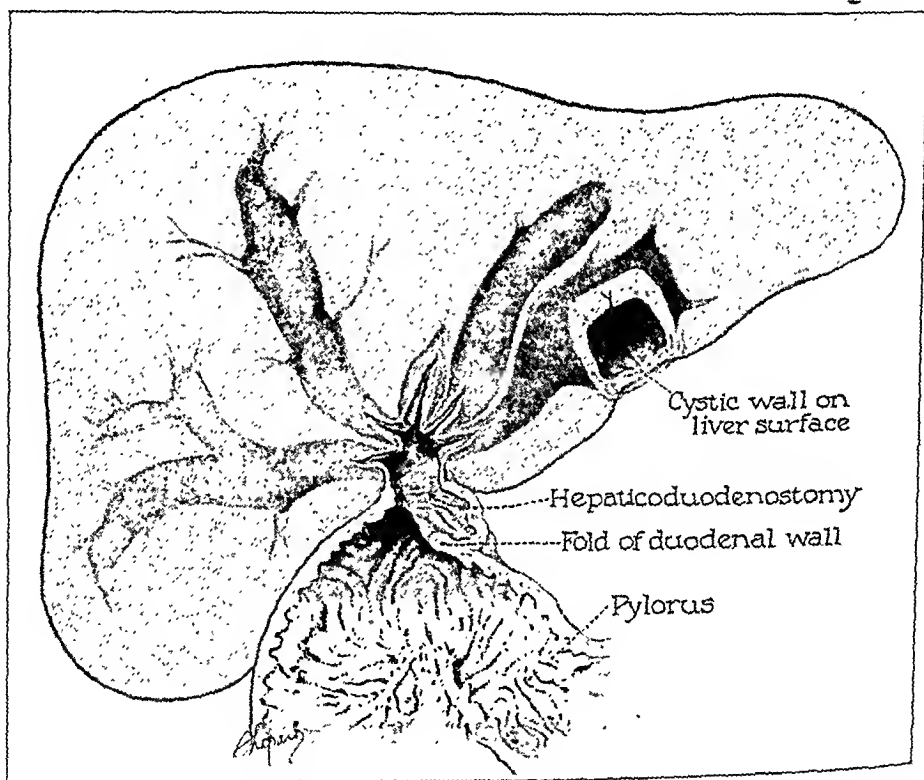
Fig. 3.—Dilatation and cystic degeneration of all the major intrahepatic bile ducts as well as the previously excised common duct. The cystic left anterior branch extended to the surface of the liver. The dilated smaller ducts were not included in the drawing but are well shown in the roentgenograms taken after ingestion of a barium meal (fig. 2). There was no evidence of stricture of the hepaticoduodenostomy stoma or complications over thirteen years after operation.

The papilla of the major duct was normal in appearance and location, 5 cm. below the minor duct, and admitted a probe 2 mm. in diameter. In spite of careful search there was no evidence of a separate papilla for the terminal end of the common bile duct or where it formerly joined the pancreatic duct. The major duct extended 1.5 cm. within the duodenal wall and 5 mm. beyond it with a perfectly normal size and appearance, when it became cystic, with a thinner wall, 2 cm. from the papilla at the same point as on the minor duct. The junction of the stenosed segment of the excised choledochus cyst was probably near the

terminal end of the dilated extraduodenal portion of the pancreatic duct. The extraduodenal junction of the common bile and pancreatic ducts, as well as their exit as separate ducts and papillae, has been observed in reported cases of choledochus cyst.

One of the first branches of the major pancreatic duct was completely stenosed, forming a large retention duct cyst with a smooth wall and occupying a large portion of the body and tail. The collapsed cyst, which had contained a clear, mucus-like material, measured 3 cm. in diameter and 9 cm. in length. Three or four small, dilated short ducts which could be probed entered the large cyst from the surrounding thin layer of the pancreatic mass.
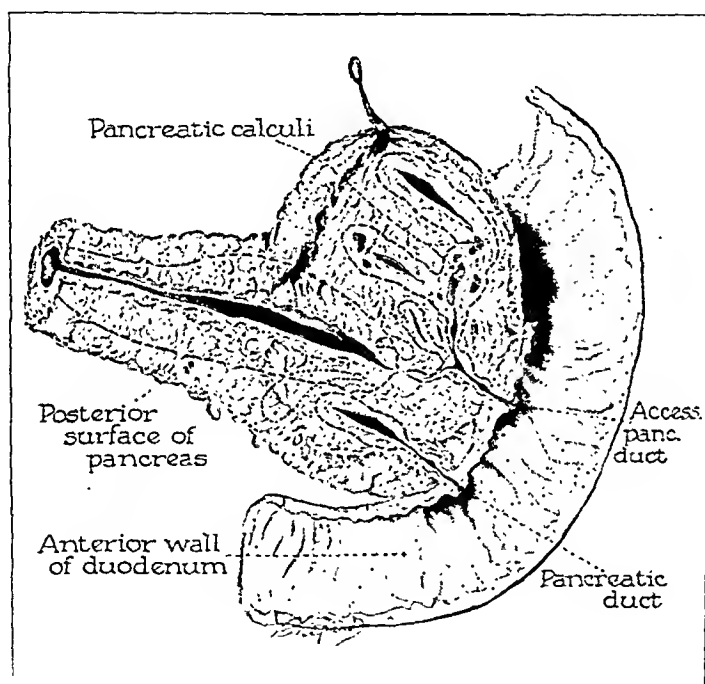
Fig. 4.—Major and minor pancreatic ducts involved in saccular dilatations and stenosis, except for their terminal 2 cm. and papilla, which were normal. Multiple calculi but no cysts occurred along the dilated saccular branches of the minor duct while retention cysts but no calculi occurred along the major duct. The parenchyma was replaced almost completely by fat and fibrous tissue.

There were three or four similar but small retention cysts distal to other stenosed branches of the major duct in the head of the pancreas, but there were no calculi in any branches of the major duct.

All microscopic sections were reviewed by Dr. Carl Apfelbach, pathologist at the Presbyterian Hospital.

Microscopic sections of the liver showed no evidence of damage or cirrhosis, and there was no dilatation or proliferation of the interlobular bile ducts. In a few places a minimal number of plasma and lymph cells were observed. There

was some postmortem dissociation of the hepatic cords, and there were occasional areas with slight fatty changes in the liver cells.

Sections of the dilated main intrahepatic bile ducts were cut, with adjacent liver tissue. The cystic walls were lined with columnar epithelium, although in places it evidently had been detached in preparation since there was no inflammatory reaction beneath the membrana propria. No muscle tissue was observed in the wall of these dilated ducts, which was composed of a wide layer of fibrous tissue. Near the largest left duct there was a large artery, and in places, parallel to it, there were numerous round and irregularly oval structures lined by cuboidal epithelium, which resembled tortuous crypts or hyperplastic glands. Serial sections showed that these structures gradually approached the dilated bile ducts, and at points their lumens were connected with the ducts. There were a few small areas of plasma and lymph cells along the walls of the dilated bile ducts.

Microscopic sections from the head of the pancreas about the branches of the major ducts showed only one round glandlike area to several low power fields and not more than ten to a whole section. Most of these areas were definitely islands of Langerhans, having a cordlike appearance, although one or two somewhat resembled acini; they had the general appearance of islands compressed by surrounding fibrous tissue. The pancreas was almost completely replaced by fat and fibrous tissue.

The wall of the large retention cyst showed absence of an epithelial layer. This also was probably caused by preparation of the sections since there was no round cell infiltration or any sign of inflammation along the thick fibrous wall.

There were no retention cysts along the dilated branches of the minor pancreatic duct, which contained calculi. In the adjacent pancreatic mass there were occasional islands of Langerhans and a few dilated and small ducts or acini lined with columnar epithelium and surrounded by fibrous tissue. Outside these ducts there were several areas consisting of a few lymphoid and numerous plasma cells, as contrasted with the branches of the major duct and the retention cysts, about which there was no inflammatory reaction.

Microscopic sections of the kidneys showed numerous hyalinized glomeruli and atrophy of approximately 15 per cent of the convoluted tubules. There was hypertrophy of the tunica media of the arcuate arteries, and in other blood vessels there were hyalinization and proliferation of fibrous tissue in the subintimal layer resembling arteriolosclerosis.

There was some inflammatory round cell infiltration where the tubules were undergoing destruction. The changes in the kidneys were typical of malignant nephrosclerosis with arteriolosclerosis of a moderate degree secondary to hypertension and arteriosclerosis such as is observed in cases of death from uremia.

COMMENT

Embryologic study of the liver and the pancreas is important to an understanding of the pathogenesis of congenital cystic dilatation and retention cysts of the bile and pancreatic ducts.

The liver is the first gland to develop and arises from the ventral anlage at about the same time that the dorsal anlage of the pancreas appears. The caudal part of the ventral anlage is hollow and gives rise to the gallbladder. It becomes constricted below by a narrow, solid cord of cells which later form the common duct and are attached to the anlage of the hepatic duct.

Two diverticula appear, one on each side of the common bile duct. That on the right becomes constricted into a cord of cells which becomes the pancreatic duct.

According to some investigators, the pancreatic evaginations are hollow. Others believe that they are solid at first. The same uncertainty exists in regard to the later outgrowths or budding into a compound tubular gland.

The left diverticulum probably disappears [2] except when it may persist as accessory pancreatic glands or diverticulums along the gastrointestinal tract or in neighboring structures, such as the gallbladder.

The small pancreas developing from the ventral anlage fuses with the larger dorsal pancreas. The ducts anastomose until those from the ventral pancreas become the major ducts to the pancreas.

The anlage of the liver develops as a series of outgrowths into the channels of the omphalomesenteric veins in the ventral mesentery. There is a series of hepatic cell trabeculae the meshes of which are filled with a sinusoidal circulation of blood. In each cord of liver cells there is a bile capillary.[2]

Lewis [3] stated that bile capillaries are present in a 44 mm. embryo. It could not be shown whether they develop as peripheral outgrowths from the periportal bile ducts or arise within the cell trabeculae as blind tubes and later anastomose to them. The latter theory would explain more satisfactorily the lack of bile capillary involvement in cystic disease of the ducts.

The common bile, cystic and hepatic ducts early become surrounded by mesenchyme, which later spreads along the ramifications of the portal vein into the substance of the liver. By the third and fourth months the bile ducts, the branches of the hepatic artery, the nerves and the lymphatics have extended into the periportal tissue.

Disturbances in the development of the mesenchyme might produce cystic dilatation of the bile ducts, although the evidence suggests maldevelopment of the ventral anlage and, in the case presented, also the dorsal anlage.

In the 47 cases which I previously reviewed [1] there was no cystic dilatation of the pancreatic ducts or evidence of polycystic disease in the kidneys, in the liver or elsewhere.

There have been numerous case reports since then,[4] but in only 1 case, in which two openings were seen in the lower end of the chole-

2. Bailey, F. R., and Miller, A. M.: Common Bile Duct: Recent Diabetes Mellitus, S. Clin. North America **12**:159 (Feb.) 1932; Textbook of Embryology, ed 5, Baltimore, William Wood & Company, 1929, p. 319.

3. Lewis, F. T., in Keibel, F., and Mall. F. P.: Manual of Human Embryology, Philadelphia. J. B. Lippincott Company, 1912, vol. 2. p. 419.

4. Wilson, H. V.: Choledochus Cyst. J. A. M. A. **95**:599 (Aug. 9) 1930.

dochus cyst and a choledochoduodenostomy was performed with the development of a pancreatic juice fistula, did the surgeon believe that there was an associated pancreatic duct cyst.[5] However, the pancreatic duct frequently joins the common duct before reaching the duodenal wall which might explain the two openings and also the pancreatic fistula. In Schloessmann's case [6] there was a second small cystic dilatation between the large one and the extraduodenal normal part of the bile duct where it was joined by the pancreatic duct, which shows the multiplicity of the cystic changes.

The occurrence of multiple noninflammatory cystic changes in the bile and pancreatic ducts with retention duct cysts in the pancreas in this case [7] constitutes a previously unrecognized pathologic entity of undoubted congenital origin. This condition usually is limited to maldevelopment of a part of the ventral anlage, but it is also evident that both ventral and dorsal anlages may be similarly and simultaneously involved and that the condition may lead to multiple retention duct cysts, at least in the pancreas. It is entirely different from polycystic disease of the liver, pancreas and kidneys, and the conditions have not been reported together.

Since polycystic disease occurs in viscera which differ in embryonic development, one may understand that cystic disease of the bile and pancreatic ducts may result from a slightly different form of maldevelopment.

Polycystic disease of the kidneys is believed to be due to maldevelopment of the metanephros and the wolffian duct with failure of union of the proximal and distal portions of the tubules.[8] Polycystic disease of the liver is not frequent, while in the pancreas it is rare, although it may occur alone or associated with similar changes in other viscera.[9]

Congenital cystic disease of the bile or pancreatic ducts should be diagnosed only when there are clinical symptoms due to stenosis with some obstruction at the outlet or having characteristic pathologic findings. Recently, Koch [10] included under this classification a case of

5. Iselin, H.: Gemeinsame Cyste der Gallen- und Pankreaswege, Arch. f. klin. Chir. **145**:304, 1927.

6 Schloessmann: Beitrag zur Kenntnis der Choledochuscysten, Deutsche Ztschr. f. Chir. **109**:161, 1911.

7. McWhorter, G. L.: Cysts of the Pancreas, Arch. Surg. **11**:619 (Oct.) 1925.

8. McGregor, A. L.: Synopsis of Surgical Anatomy, ed. 3, Baltimore, William Wood & Company, 1936, p. 344.

9. Wood, H. G.: Polycystic Disease of the Pancreas: Report of a Case, Proc. Staff Meet., Mayo Clin. **11**:449 (July 15) 1936. Walters, W., in discussion on papers by Wood, Rynearson, Kepler and Walters and Mayo, ibid. **11**:45 (July 15) 1936. Nygaard, K. K., and Walters, W.: Polycystic Disease of the Pancreas (Dysontogenetic Cyst), Ann. Surg. **106**:49 (July) 1937.

10. Koch, F.: So-Called Choledochus Cyst (Idiopathic Congenital Dilatation), Hygiea **98**:577 and 608 (Sept. 15) 1936.

dilatation of the common duct with no obstruction found at the time and another case with an obstructing tumor of the papilla.

As to the cause, it has been suggested that the stricture of the terminal bile duct is a form of congenital atresia and that the dilatation is secondary to the incomplete obstruction. Beneke [11] found in a review of cases in which there was complete congenital obliteration of the common bile duct that the extrahepatic ducts were not dilated. There may be exceptions to this finding, as in the cases of Legg and Oxley.[12]

Budde [13] concluded that cystic dilatation of the common duct was secondary to primary diverticula of the pancreatic anlage and was similar to traction diverticula. In his case there was a diverticulum of the duodenum, into which the strictured common duct and the pancreatic duct both entered.

Morley [14] stated that a valvular obstruction of the bile duct just outside the duodenum results from deficient peritoneal fixation. Pavel [15] has suggested that spasm of the sphincter is the cause of congenital cystic dilatation of the common duct, but the evidence does not support this theory.

The absence of muscle fibers in the dilated ducts in my case may have been due to a congenital deficiency leading to dilatation or resulting from it. It is recognized that there may be a similar deficiency of smooth muscle in the presence of congenital hydronephrosis or hydronephrosis of acquired mechanical origin and that congenital defects of smooth muscle which occur in the wall of the arteries at the base of the anterior part of the brain may result in congenital aneurysms and later in hemorrhages.[16]

Another congenital factor may be maldevelopment of mesenchymal tissue about the bile ducts, of a segmental nature, leading to both stenosis and dilatation. Further understanding may depend on a complete knowledge of the embryologic development of the bile and pancreatic ducts.

11. Beneke, cited by Roberts, E. D.: Un cas de dilatation kystique du canal cholédoque, Thesis, Lausanne, 1914.

12. Legg, J. W.: Congenital Deficiency of the Common Bile Ducts Ending in a Blind Sac; Cirrhosis of the Liver, Tr. Path. Soc. London **27**:178, 1876. Oxley, M. G. B.: Congenital Atresia of the Duodenal Opening of the Common Bile Duct in an Infant, Producing a Large Abdominal Tumor, Lancet **2**:988 (Dec. 8) 1883.

13. Budde, M.: Ueber die Pathogenese und das Krankheitsbild der cystischen Gallengangserweiterung; sogenannte idiopathische Choledochuscyste, Deutsche Ztschr. f. Chir. **157**:364, 1920.

14. Morley, J.: Congenital Cyst of the Common Bile Duct, with Report of Two Cases, Brit. J. Surg. **10**:413 (Jan.) 1923.

15. Pavel, I.: Jaundice Caused by Functional Obstruction, J. A. M. A. **110**: 566 (Feb. 19) 1938.

16. Apfelbach, C., pathologist of the Presbyterian Hospital: Personal communication to the author.

In the case here presented the maldevelopment of the bile ducts and both pancreatic ducts, not involving their dudoenal terminations, indicates the involvement of both ventral and dorsal anlages. This condition primarily apparently did not involve either the peripheral interlobular bile capillaries or the peripheral pancreatic ducts and acini although the latter secondarily were almost completely degenerated.

Symptoms of congenital cystic disease of the bile and pancreatic ducts were variable, owing to the differing degrees of stenosis and complications.

Clincially one must differentiate the symptoms of cystic disease of the ducts from obstruction of the common duct by calculi, inspissated bile or mucus, which may occur together with congenital stenosis [17] and from complete atresia of the ducts. The small stature of my patient was probably the result of a restricted food intake from infancy.

Pathologically such dilatation must be differentiated from dilatation of the common duct produced by an acquired obstruction.[18]

Clinically, it may be difficult to diagnose involvement of the pancreatic ducts either with or without true retention cysts. Large retention cysts may be palpable or may produce pressure disturbances, and there may be symptoms or laboratory evidence of complications or extensive degenerative changes. Calculi which may cause attacks of pain and evidence of inflammatory changes in the pancreas may be visualized by roentgenograms.

The fibrous and fatty degenerative changes in the pancreas with loss of function resulting from congenital occlusion of the ducts, the retention cysts and the obstructing calculi were probably contributing factors in the development of diabetes, arteriosclerosis, hypertension and nephrosclerosis leading to death, but there was no evidence of permanent disturbance of function or of pathologic change in the liver.

At the time of the hepaticoduodenostomy the patient was in no condition to withstand any operation on the pancreas even if it had been desirable. One should consider what benefits might have been obtained from drainage of the large pancreatic cyst by creation of an anastomosis with the small intestine or by removal of the calculi. If such an operation had been performed before extensive degenerative changes had occurred, some islands of Langerhans and some pancreatic function might have been preserved. However, the possible benefits, especially after a number of years, might be offset by the risk of operation.

In the 47 cases of cystic dilatation of the common bile duct which I reviewed in detail,[1] biliary cirrhosis was noted in 14; the liver was

17. Ladd, N. E.: Congenital Obstruction of the Bile Ducts, Ann. Surg. **102**: 743 (Oct.) 1935.

18 Counseller, V. S. and McIndoe, A. H.: Dilatation of the Bile Ducts (Hydr. hepatosis), Surg., Gynec. & Obst. **43**:729 (Dec.) 1926.

normal in 12 and was not mentioned in 13, while in the others a moderate degree of hepatitis was described.

In contrast to this group with incomplete or intermittent biliary obstruction, Beneke [11] reviewed a series of cases with complete congenital obliteration of the common duct and reported observation of cirrhosis of the liver in all.

There have been few reports of cases with hepaticoduodenostomy of several years' duration for any condition, and necropsy observations have usually been reported on those in which the results were unsuccessful.

Normally the sphincter and papilla guard the bile ducts from ascending parasites, foreign bodies and infection.[19] Both clinical and experimental results of hepaticoduodenostomy have shown the dangers from stricture formation and ascending infection, although it is probable that the latter would rarely have occurred without biliary obstruction. Recent experimental work of Gentile [20] has indicated that danger of ascending infection in hepaticoduodenostomy in the absence of biliary stasis has been overemphasized. However, a certain amount of regurgitation of food through the stoma is always a potential source of infection and may produce mild attacks of inflammation in the ducts or liver, with complete recovery. In animals I have observed death following obstruction of the common duct by roundworms after experimental dilation of the sphincter with patency of the outlet.

Finsterer [21] stated that he has abandoned drainage of the hepatic ducts for anastomosis of the common duct to the duodenum in cases of multiple stones in the hepatic duct, in the presence of severe suppurative cholangitis and in the presence of absolute or relative stenosis of the papilla. He reported 80 cases with an increase of cures from 40 to 95 per cent for as long as ten years without ascending infection in spite of a wide anastomosis, which he sometimes demonstrated by roentgen ray visualization after administration of a barium sulfate meal.

The prognosis of cystic dilatation of the common bile duct without operation is usually bad. The friable condition of the stenosed terminal segment of the common bile duct and the surrounding edema in my case would indicate some inflammatory reaction during attacks of obstruction. This may explain the usual progressive nature of the stenosis and biliary obstruction in the absence of suppuration. In 48 cases [1] the

19. McWhorter, G. L.:   The Surgical Significance of the Common Duct Sphincter, Surg., Gynec. & Obst. **32**:124 (Feb.) 1921.

20. Gentile, A.:   Cholecystogastrostomy and Hepatitis: Experimental Study, Arch. Surg. **30**:449 (March) 1935.

21. Finsterer, B. F., in discussion on Bernhard, F.:   Ueber neuere Gesichtspunkte aus der Chirurgie der Gallenwege, Arch. f. klin. Chir. **189**:81, 1937; abstracted, Surg., Gynec. & Obst. **65**:412 (Nov.) 1937.

operative mortality was 71 per cent, and all patients not operated on died. The high mortality after operation was due to the fact that most of the patients were emaciated and badly jaundiced.

In 22 cases exploratory operation, alone or combined with external drainage, resulted in death. Exploratory aspiration with leakage of bile and peritonitis occurred in 2 cases.

The mortality was fairly low in cases in which biliary drainage was obtained by an anastomosis of the cystic common duct to the duodenum at the first operation. In more recent operations by this method the mortality has been much lowered by earlier operation. However, the stoma must be adequate, as stenosis has resulted, producing attacks of pain and jaundice sometimes so severe as to require reoperation.

The operative treatment of choice is either to anastomose the common bile duct to the duodenum or to excise the dilated part of the common duct and anastomose the remaining end to the duodenum.

The former is the simpler and has a relatively low operative mortality, and it should be chosen when the patient is in poor condition, but the remaining cystic common duct may cause prolonged retention of food. This may lead to severe ascending cholangitis, as in the fatal case reported by Fowler,[22] in which a lateral anastomosis of an acquired dilatation of the common duct was made to the duodenum.

Complete or partial excision of the dilated common duct with an anastomosis of the stump to the duodenum may be chosen when the cystic dilatation is large and the patient is in good condition, since, as shown in the present case, there will be little retention of food and less danger of cholangitis.

Nonoperative treatment of the pancreatic duct calculi and retention cysts in this case had no obvious direct effect on the outcome, but the obstruction of the ducts by cysts and calculi undoubtedly produced degenerative changes in the pancreas, contributing to loss of function, diabetes and arteriosclerotic changes.

Indications for operation on the pancreas might result from pain from pancreatic calculi, secondary suppuration and physiologic or pathologic disturbances from retention cysts.

SUMMARY AND CONCLUSIONS

A necropsy report is made of a case of congenital cystic disease of the bile and pancreatic ducts.

This condition is shown to be a distinct congenital entity which may involve both ventral and dorsal anlages but is not to be confused with congenital polycystic disease of the liver or the pancreas.

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22. Fowler, R. S.: Choledochus Cyst. Ann. Surg. **64**:546 (Nov.) 1916.

In this case the findings point to a congenital maldevelopment of anlages which form the bile ducts and both pancreatic ducts. In other cases these changes were largely limited to involvement of the extra-duodenal portion of the common bile duct, although in some cases it distorted secondarily the intraduodenal portions by traction, distention or inflammation. Apparently in no instance were the peripheral capillary bile ducts involved. In the present case, the pancreatic acini and islands of Langerhans were almost completely degenerated. evidently as a result of congenital obstruction of the ducts and pressure by the retention cysts or of the presence of calculi.

The liver showed no evidence of cirrhosis, and no complications appeared for over thirteen years after a hepaticoduodenostomy, which is evidence that ascending infection will not necessarily result from the operation and that hepatic function may not be damaged in the absence of biliary obstruction, even with regurgitation of food into the intra-hepatic ducts.

Through further knowledge and early clinical recognition a properly chosen operative procedure may lessen the dangers of this congenital condition at a minimum risk.

CLINICAL SIGNIFICANCE OF CALORIMETRIC CHANGES IN THE LOWER EXTREMITY

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AND

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Hesse [1] in 1929 directed attention to the occurrence of calorimetric changes in the skin of the lower extremity, resulting from irritation or pressure on the lumbar portion of the ganglionated cord and its connecting rami. Pressure or irritation affecting the lumbar portion of the ganglionated cord, whether it is of inflammatory or of neoplastic origin, may produce well defined changes in temperature of the skin of the corresponding lower extremity.[2]

The changes in temperature vary with the degree and type of pressure on the ganglionated cord. Mild pressure or irritation results in the appearance of increased vasoconstrictor phenomena in the corresponding lower extremity. Comparative estimations of the temperature of the skin of the lower extremity will disclose in such instances a decrease in temperature on the side on which retroperitoneal pressure is present. The increased vasoconstriction results in lessened blood volume and thus in lowering of the cutaneous temperature. Paralleling the changes in the surface temperature are changes in the sweat glands and in the erector pili muscles. In the stage associated with peripheral vasoconstriction, perspiration and the pilomotor reflex are increased.

When pressure on the ganglionated cord is sufficient to interrupt the conduction of all impulses that traverse the cord, persistent vasodilatation results, and the temperature of the corresponding lower extremity is elevated. During the stage of peripheral vasodilatation, perspiration

and the pilomotor reflex are decreased. Additionally, the stage of vaso-dilatation shows an absence of the waves of spontaneous diminution of volume.[3]

The differences in temperature between the two extremities may range from 1 to 6 degrees C. (1.8 to 10.8 degrees F.). The difference in temperature encountered in the lower extremities during the stage of increased vasoconstriction is generally less than that observed during the stage of vasodilatation.

Determinations of temperature were carried out in the following manner: The lower extremities were examined for evidence of peripheral vascular disease which might influence cutaneous tempera-ture. All 3 patients had adequate peripheral circulation. The lower extremities were exposed to room air, the rest of the body being covered only by a light sheet. Care was taken that there should not be any drafts or movements of air which might influence the temperature of one or both extremities. The temperature of the first and third toes of each foot was taken with an electrothermocouple at the start and at intervals up to thirty minutes' exposure to room air. It was assumed that at the end of thirty minutes the effect of previous warming of the extremities by bed clothes had been eliminated. In the absence of an electrothermocouple the temperature of the skin may be taken by the simultaneous use of two thermometers at corresponding sites on the lower extremity, preferably between the toes. Differences in tempera-ture of the lower extremity of 1 degree C. (1.8 degrees F.) or more can be felt with the bare hand.

REPORT OF CASES

CASE 1.—E. H., a man aged 52, was admitted to the hospital on Dec. 29, 1935, because of severe constipation of two months' duration and cramps in the lower part of the abdomen for about three weeks. There had been no loss of weight. The most important finding at physical examination was a mass in the right lower quadrant of the abdomen, about 6 cm. square. It was hard, fixed and not tender. There was a small epigastric hernia. A barium sulfate enema revealed a complete obstruction to the barium at the proximal transverse colon. The diagnosis of the roentgenologist was carcinoma of the transverse colon. Laboratory studies gave normal results. The temperature studies were as follows:

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
25.2 C. (77.4 F.)	23.5 C. (74.3 F.)	22.5 C. (72.5 F.)	21.5 C. (70.7 F.)

Laparotomy was performed by means of a transverse incision on the right side, at the level of the umbilicus. The posterior paries was found attached to a hard mass the size of a fist, apparently springing from the transverse colon. The mass was attached to the liver. There were nodules in the peritoneum. The mass

3. Bolton, B.; Williams, D. J., and Carmichael, E. A.: Sympathetic Ganglionic Responses in Man. Brain 60:59 (March) 1937.

was partly freed but was found to be inoperable. A biopsy of material taken from the omentum revealed secondary carcinoma.

Comment.—In this patient the temperature of the extremity was higher on the side on which the lesion was present.

CASE 2.—B. S., a man aged 65, was admitted to the hospital Jan. 8, 1936, because of vomiting after every meal and epigastric pain of several months' duration. There had been no loss of weight. About six weeks before admission the patient observed that the right thigh was larger than the left and was painful. He also had pain in the right lower quadrant of the abdomen. The medical history was irrelevant. On physical examination the only positive findings were tenderness to deep palpation in the right lower quadrant of the abdomen, varicose veins, especially on the right leg, and enlargement of the right thigh. No definite mass was palpated in the abdomen. Cystoscopic examination, retrograde pyelographic study and roentgenographic examination of the thigh gave negative results. A barium enema disclosed "the cecum lying unusually high, being apparently displaced upward by an intrinsic mass." The results of urinalysis, blood counts and chemical studies of the blood were normal. The surface temperature was as follows:

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
30.2 C. (86.4 F.)	30.09 C. (86.2 F.)	24.8 C. (76.6 F.)	23.6 C. (74.5 F.)

Laparotomy was performed, and a mass of retroperitoneal lymph nodes was found lying against the sympathetic ganglions on the right side.

Comment.—If the temperature is higher on the affected side the ganglions are destroyed or impulses completely interrupted.

CASE 3.—I. C., a man aged 26, was admitted to the hospital May 8, 1935, because of pain in the lower part of the abdomen and diarrhea since November 1934. He had had vague symptoms dating back to March 1933. The medical history revealed incision of a cervical gland at the age of 9 and also the development of a sinus in the left ankle in infancy, which was diagnosed as tuberculosis. On physical examination the outstanding finding was the presence of a mass palpable in the right lower quadrant of the abdomen. Digital rectal examination revealed a hard, fixed shelving against the anterior wall of the rectum. Sigmoidoscopic examination confirmed the presence of this bulge in the rectal wall, and beyond it, at the rectosigmoid junction, resistance was met. A barium enema likewise revealed an obstruction at the rectosigmoid junction. The diagnosis was carcinoma of the sigmoid or retroperitoneal sarcoma. Laboratory studies, including search for tubercle bacilli, all gave negative results. Temperature studies revealed the right foot to be distinctly warmer than the left.

Right Foot		Left Foot	
First Toe	Third Toe	First Toe	Third Toe
26.2 C. (79.2 F.)	25.8 C. (78.4 F.)	22.4 C. (72.3 F.)	21.7 C. (71 F.)

Laparotomy was then performed, and an enormously thickened terminal ileum was found. It was adherent to the peritoneum, the sigmoid flexure, the transverse colon and other structures. Twelve inches (30 cm.) of the terminal portion of the ileum and part of the cecum were resected. The patient had an uneventful convalescence and was discharged two weeks after operation. The pathologic

diagnosis was that of a chronic inflammatory process of the ileum. At the time of writing, three years after the operation, the patient has no symptoms. Temperature studies in 1938 revealed the right foot still approximately 1 degree C. (1.8 degrees F.) warmer than the left.

<div align="center">COMMENT</div>

The clinical findings noted are in accord with the anatomic structures and physiologic functions of the affected parts. A brief discussion of the physiologic considerations is set forth.

The ganglionated cord lies fixed along the anterolateral surface of the vertebrae, and any pressure on the cord, such as may be caused by inflammation or by a neoplasm, may produce changes in the temperature of the ipsilateral lower extremity. The fixed retroperitoneal location of the ganglionated cord renders its component neurons and fibers readily liable to retroperitoneal irritation or pressure.

The function of the sympathetic innervation of the blood vessels is essentially tonic or excitatory. The ganglions of the lumbar portion of the ganglionated cord probably contain the cell bodies of the vasomotor postganglionic fibers which act as vasoconstrictors. The peripheral blood vessels receive their efferent innervation solely through the sympathetic system; their supply by parasympathetic fibers is still a moot question.

It is generally accepted that vasomotor responses are easier to obtain from the toes than from the fingers. Immersion of the lower extremity in water at 44 to 45 C. (111.2 to 113 F.) produces a sustained, widespread dilatation of the cutaneous vessels of the digits, and the resultant changes in the blood volume are greater in the toes than in the fingers. Similarly, peripheral sensory stimuli effect a greater degree of vasoconstriction in the toes than in the fingers. Examination of patients who have been sympathectomized for nonvascular diseases shows absence of spontaneous waves of diminution in the toes which would seem to imply that waves of diminution in the blood volume of the toe are an indication of vasoconstriction and are dependent on the integrity of the postganglionic fibers.

It is needful to bear in mind that pure ganglionic vasomotor responses do not occur. To effect a vasomotor response under normal conditions it is necessary for an afferent fiber to reach the spinal cord and within the central nervous system to be connected directly or indirectly by connector neurons to the cells in the intermediolateral column of the spinal cord, which give origin to the preganglionic fibers.

The postganglionic fibers in the case of the blood vessels are under the control of the regulatory, inhibitory preganglionic neurons. Thus, persistent dilatation of the blood vessels may result from destruction or pressure of the preganglionic fibers. Persistent dilatation of the vessels

of the toes may result from interruption of either the preganglionic or the postganglionic fibers to the toes.

One sometimes wonders whether the greater vascular stability of the upper extremity as compared with the lower extremity may not be the result of simultaneous action of two preganglionic fibers on a single postganglionic neuron, reenforcing or "stepping up" the inhibitory impulse. Perhaps the absence of a white rami communicans in the lower three lumbar nerves may account for this difference in vascular stability.

This calorimetric syndrome appears to be based on sound premises. Clinically it has received meager attention.

A lesion causing enlargement of the kidney, a lesion of the vertebrae, a retroperitoneal lesion (such as lymphadenitis, sarcoma or metastasis) or an intra-abdominal lesion associated with fixation of the posterior parietal peritoneum may produce irritation or pressure of the lumbar portion of the ganglionated cord. In brief, any lesion which causes pressure or irritation of the lumbar portion of the ganglionated cord may effect changes in the temperature of the ipsilateral lower extremity. Retroperitoneal lesions not infrequently present an obscure clinical picture, and any possible aid toward early diagnosis is worth while.

Comparative calorimetric studies of the cutaneous temperature of the lower extremities may be helpful not only in diagnosis but in localization of the lesion, since the changes occur on the side on which retroperitoneal pressure is present. In addition, information may be obtained as to the stage and progress of the lesion. Irritation or moderate pressure on the lumbar portion of the ganglionated cord produces peripheral vasoconstriction with its accompanying decrease in the cutaneous temperature on the side on which the retroperitoneal pressure is present. As the lesion increases in size, vasoconstriction is succeeded by vasodilatation, which is associated with elevation of temperature and absence of the waves of spontaneous diminution of volume.

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HISTOLOGIC AND HISTOCHEMICAL STRUCTURE OF THE NORMAL THYROID GLAND

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The study of the structure of the normal thyroid gland has been strangely neglected. So long as the morphologic character of the goitrous gland was just one more thing to quarrel about, this lack of knowledge of the normal gland was not a serious matter. Now that the relation of the goitrous gland to the heart has been abundantly demonstrated in the clinic, knowledge of the anatomy of the nongoitrous gland becomes an imperative necessity. The question is whether or not a nongoitrous gland may so degenerate as to affect the heart as a goitrous gland does. In order to answer this question it will be necessary to examine a large number of thyroid glands of nongoitrous persons.

Goiter is a clinical term. This becomes important in the morphologic study when one attempts to compare the nongoitrous and the goitrous gland. Even in the laboratory it is often a question whether a particular thyroid is goitrous. To determine this by weight alone is, of course, impossible. If one attempts to determine it by microscopic study one finds the dividing line equally indistinct. The confusion is heightened when one finds in a supposedly normal gland changes indistinguishable from those found in goitrous glands with associated cardiac symptoms which disappear when the gland is removed. This suggests the possibility that if one encounters in patients with nongoitrous glands cardiac disease identical with that found in association with degenerating goiter one must remove the thyroid gland in order to rescue the heart.

Clinically the presence of goiter is determined by palpation of the neck. Whether or not a diagnosis of goiter is made depends on the location of the gland, the type of patient and finally the "personal equation" of the examiner. Failure to diagnose a goiter clinically is never conclusive evidence that no goiter is present.

Rice [1] has presented a discussion of the normal thyroid gland. He has found the infantile gland divided into fields and the adult gland made up of acini of various sizes, lined by flat epithelium. He has

1. Rice, C. O.: Histologic Structure of the Normal Thyroid Gland: Variations and Their Significance in the Interpretation of Pathologic Conditions of the Thyroid Gland, Arch. Surg. 36:96 (Jan.) 1938.

stated that in the gland of the aged the connective tissue septums again become prominent.

The present article is intended to be confirmatory and in a measure supplementary to that of Rice: confirmatory in the points previously mentioned; supplementary, chiefly because of the fact that I have given particular attention to a study of the colloid by means of tinctorial chemical tests. Studies by others have dealt chiefly with the epithelium. The varied and changed structure of the colloid seems to me to hold the key to what the gland is actually doing. "By their acts ye shall know them" is accepted by the ecclesiastic, the policeman and the physiologist. Why should the surgical pathologist not apply the same criterion? The present determinations indicate that such a study is particularly valuable, because it gives the investigator a new "slant" on the functions of the cell, or at least it helps him to determine when the cell ceases to function. First of all, a tinctorial study of the colloid compels one to doubt whether cells once quiescent become active again. That is to say, a "resting" cell is probably permanently functionless. If there is a return of function in the gland it is by the agency of newly formed acini.

My studies began forty years ago. I have endeavored to secure as much fresh material as possible, either in the course of operations in the cervical region or at autopsies on patients who had met violent death or who had died from some sudden complication, notably from hemorrhage. The purpose of thus selecting the material is to avoid confusion caused by changes in the structure of the thyroid, incidental to a terminal disease.

I was at first disposed to believe, from a study of this carefully selected material, that it differed in no way from that secured at routine autopsies. Apparently the disease which causes the death of the patient produces no regular change in the structure of the gland. However, a more extended study of autopsy material compels me to believe that at least exhaustive diseases, such as suppurations, may hasten the changes that one ordinarily finds in the glands of the aged. The structure is so variable in chronic disease as well as in old age that no definite conclusions can be reached. This is not surprising, because the calendar only in a general way indicates the actual age of the patient. Perhaps one is as old as one's thyroid gland. This problem is well worth further attention if physicians are to study the nongoitrous thyrotoxic heart.

Generally speaking, one can divide the study of the normal thyroid into three parts: the normal thyroid in childhood, the normal thyroid in maturity and the normal thyroid in old age.

Childhood may be made to include the period between the embryologic appearance of the gland and the end of puberty. Young folk in their teens regard themselves as mature, despite the opinion of their elders, and a study of their thyroids compels one to agree with them.

The characteristics of the immature gland are a relatively high epithelium and a thin colloid. Beginning as solid cell masses, acini gradually form, until after puberty few or no solid interacinal cell masses remain. In general, one may compare the gland in this early stage of its development with the thyroid of a patient with exophthalmic goiter. The nervous activity of the toxic stage compares well with the restlessness of childhood. A study of the thyroid provides an explanation. In both instances the acinal cells are cuboidal, even columnar, and the colloid is invariably thin. The height of the cells varies, but they are always at least as high as they are broad.
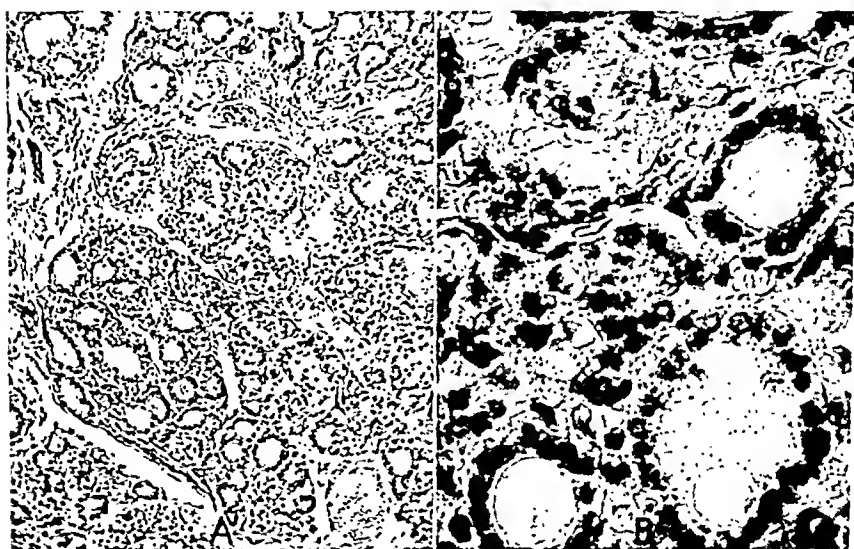
Fig. 1.—Thyroid of a child aged 7 months. *A*, fibrous tissue bundles dividing the area into fields; *B*, well formed acini containing thin colloid. Between are masses of cells showing solid masses or the beginning of acini.

The infantile gland is characterized by heavy columns of fibrous tissue which divide the gland into fields. It appears as though the gland is provided with enough connective tissue to supply it in its adult size. The arrangement of these connective tissue bundles gives the examiner a clue as to why nodular enlargements are found in goiters.

The embryo gland cells form solid masses from which in time the acini develop. In the early stages one finds some areas in which definite acini have formed, while in others solid masses remain. The acini vary much in size and in the nature of the contents (fig. 1). One finds statements in the literature to the effect that in the early glands the epithelium stains badly and is sometimes exfoliated. This impression is due to the difficulty of securing fresh material for examination.

One still occasionally finds statements that some of the acini are empty. It would be surprising if this were true, because an empty cavity elsewhere in the body is unknown. If a fluid-containing sac is deprived of its fluid the walls collapse. I believe it can be confidently stated that if the acinus appears to be empty one of two conditions is present: Either the acinal content is so thin that it refuses the dye, or the colloid has fallen out in the process of preparing the slides. The former is proved by the fact that acinal content which refuses the ordinary dyes accepts special dyes. In the infantile gland, for·instance, there are no empty acini if Mallory's aniline blue stain is used. On the other hand, if the same material is hardened in solution of formaldehyde it may show no empty acini, while a neighboring block fixed in Zenker's solution may show many "empty" acini. Furthermore, if one mounts a section fixed in Zenker's solution in the regular way and compares it with a fellow slide which has been shaken or penciled, the latter will show many more empty acini. It is not unusual in slides which show many empty acini to find disks of colloid floating about, which have become detached in the process of staining. Naturally, the acinus from which such a disk has been dislocated is "empty." Furthermore, colloid-embedded sections of the same tissue show no empty acini whatever. Of·course one finds vacuoles in many thyroid acini, both normal and diseased. What is in a vacuole no one has stated so far as I know, but it is logical to assume that it is some substance that refuses any stain.

Rice wisely refused to discuss the question as to whether there are interstitial cells but pointed out that sometimes there are such and sometimes not, a perfectly obvious fact. In any gland, in childhood, clumps of cells are found between well formed acini which contain no lumens and consequently no colloid (fig. 2). In well preserved tissue this transition can be easily followed—well developed acini, beginning acini containing a little colloid and clumps of cells showing no lumens.

In older children the proportion of acini to cell clumps increases, but until puberty some clumps remain, the acini are lined with cuboidal epithelium and the colloid is thin.

The gland of the young adult is entirely different. The epithelium of the acini is flat and is for the most part uniform. There may be division into lobules by prominent bundles of connective tissue (fig. 3 *A*). The colloid is homogeneous and stains uniformly with eosin (fig. 3 *B*), coloring it just as it does red blood corpuscles. This normally staining colloid may be taken as the sign of the adult period. For the most part the connective tissue is sparse in the adult and is scarcely perceptible unless stained with specific dyes.
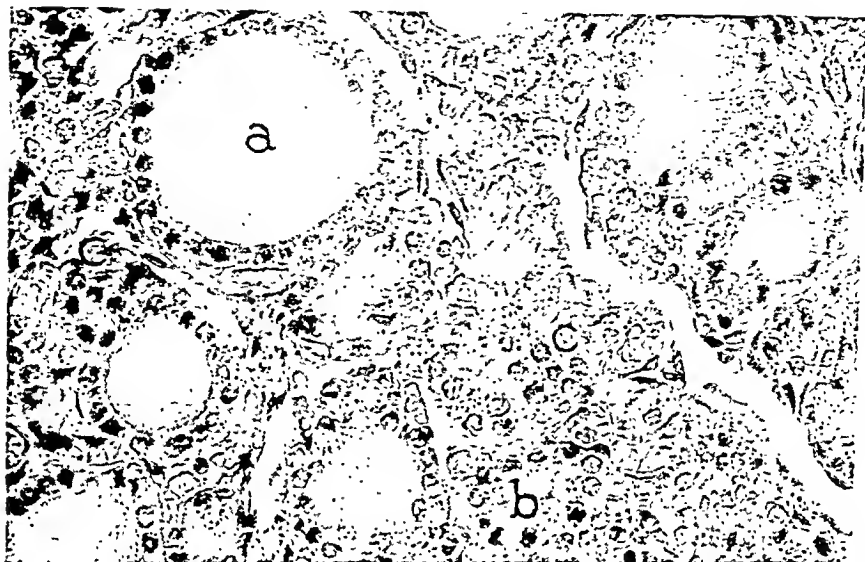
Fig. 2.—Thyroid of a premature child: *a*, well formed acinus containing uniform but palely staining colloid; *b*, very small acinus containing a very little colloid; *c*, clumps of cells without lumens.
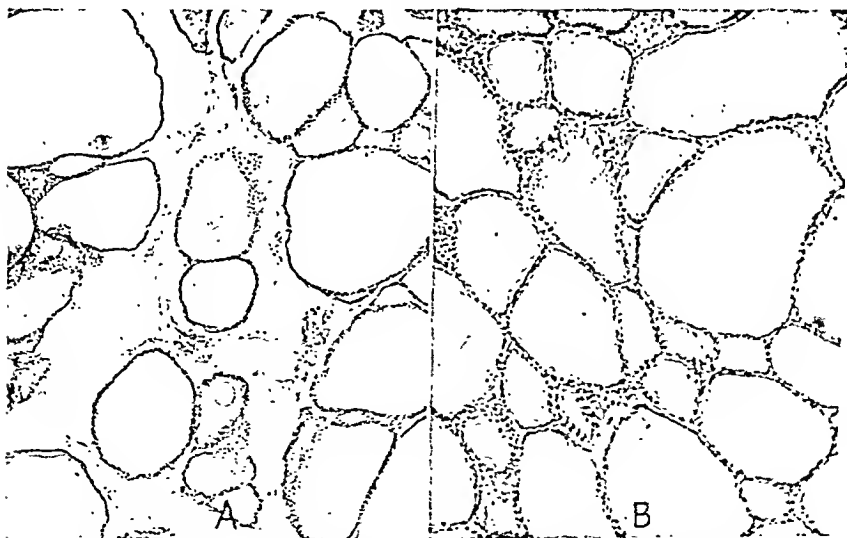
Fig. 3.—Thyroid from a man aged 22. *A*, acini separated by abundant connective tissue. The acini are lined with flat cells and are filled with a uniform colloid. *B*, scattered clumps of cells between the acini.

Many slides show no interacinal cells, but in some specimens such cells are uniformly present throughout the section (fig. 4). Whether these are but vestiges of the infantile stage, as I believe, or have some other significance is at present impossible to say. Patients who have them exhibit some of the nervousness of childhood. On the other hand, some slides of material from patients in early life, even adolescence, show here and there an acinus indicating the degeneration usually found only in mature persons.

In the gland of an aged person, meaning any one beyond the age of 40, the changes encountered are numerous. They involve the connective tissue, the epithelium and particularly the colloid. These may be exam-
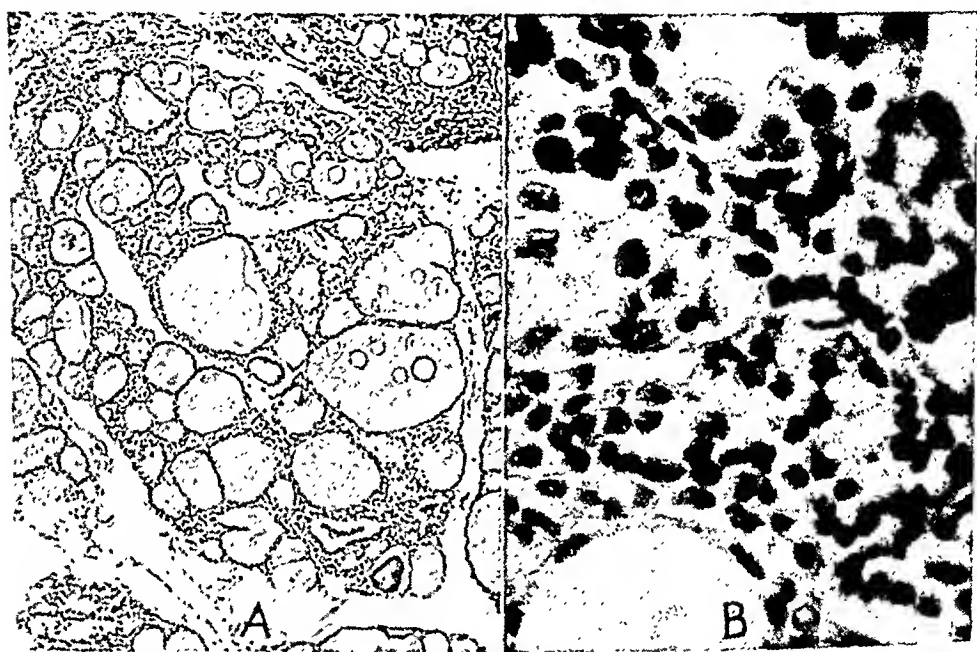
Fig. 4.—Material from a thyroid, showing interacinal cells. *A,* large acini lined with flat epithelium; *B,* interacinal areas filled with a mass of cells without a definite acinus formation (some are lymphoid cells but the larger number resemble those of fetal glands).

ined in turn. It may be stated at the outset that for the most part the changes are frankly regressive.

The constant change of the acinal cells is flattening, even to disappearance (fig. 5 *B*). With this atrophy of the cells, if one may call it such, there is constantly associated a change in the colloid (fig. 5 *A*). This change in the colloid is shown by its refusing the eosin in the usual laboratory stain and accepting the hematoxylin. In other words, it has become basophilic. Before the change can be demonstrated by this simple stain, special stains show it. For instance, the colloid stains orange in Mallory's aniline blue stain before it accepts the hematoxylin.

When this is the case the colloid is always basophilic. The age at which this flattening of the epithelium and change in the colloid occur is not constant. One may find some basic colloid in young persons, but usually it appears only in middle age, and it may be absent even in the aged.

In the aged the acini sometimes tend to reproduce themselves but succeed only in producing small acini with flat cells or in forming clumps of cells without lumens and hence with no evidence of colloid (fig. 6). The function of these newly formed acini, if they are such, is not known. One can say only that in the small acini, which probably represent attempts at reproduction, the cells are irregularly placed, in many filling
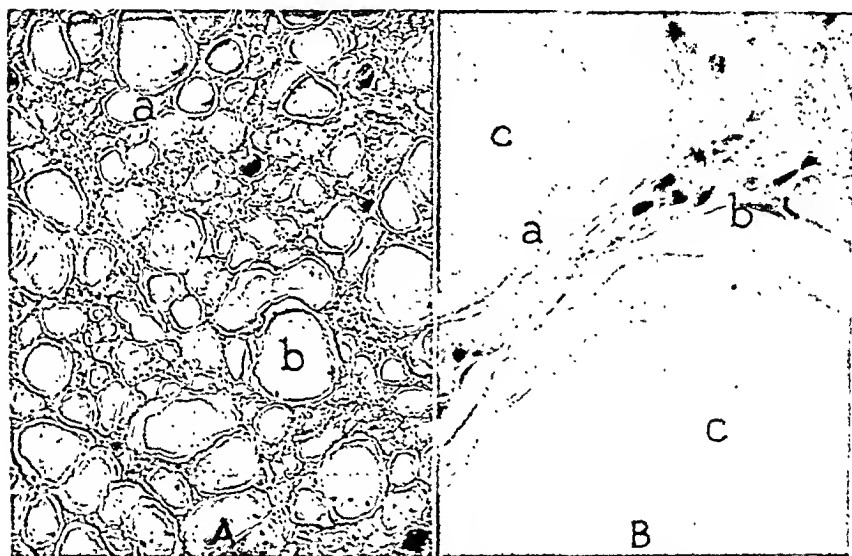
Fig. 5.—Thyroid of an adult. *A*, acini of varying size and staining: *a, normal colloid; b,* colloid stained with hematoxylin. *B,* acini with loss of epithelium; *a,* walls of acini without epithelium; *b,* flattened cells; *c, c,* colloid stained with basic stain.

the entire lumen. The structure of these cells seems identical with that of the cells in Hashimoto's struma.

In some cases this aimless attempt at reproduction is even more pronounced. Solid cell masses may give way to cells irregularly placed (fig. 7 *A*). When this irregularity is present and the connective tissue is abundant the condition is sometimes diagnosed as malignant (fig. 7 *B*). These changes are found most commonly in old goitrous glands.

The changes incident to age are better traced in the colloid than in the epithelium. If there are basophilic changes in the colloid one may class the patient as aged whether such changes have been brought about by the passing of the years or by some disease. It is possible that such changes
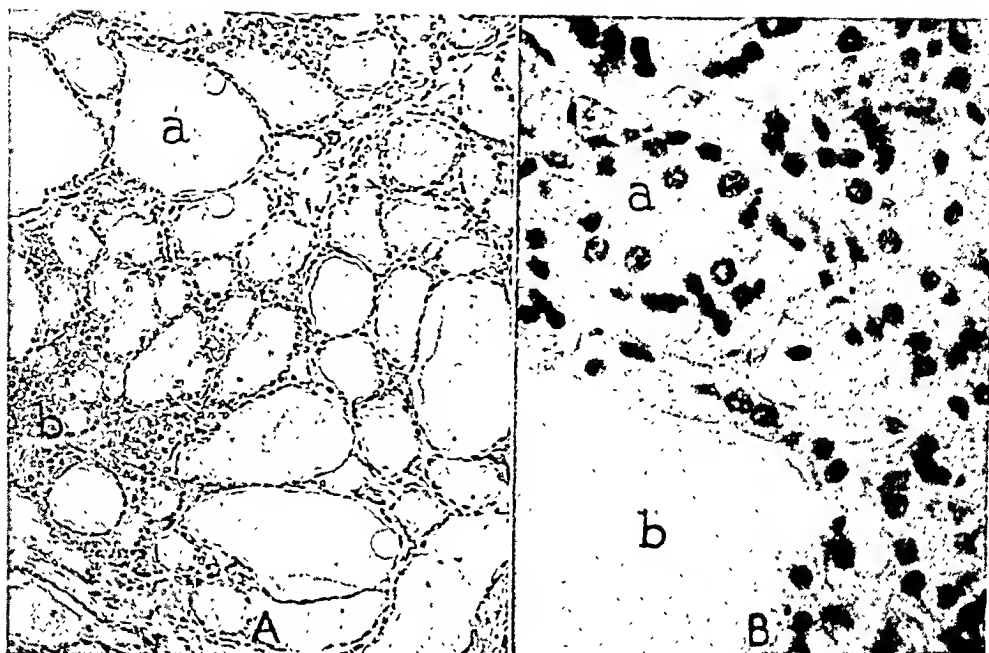
Fig. 6.—Thyroid from M., aged 63: *A*, relatively normal colloid; *a*, acini lined with flat cells; *b*, clumps of cells between the acini. *B, a*, cell clumps without lumens; (the cells are granular); *b*, acinus lined with partly defective epithelium.
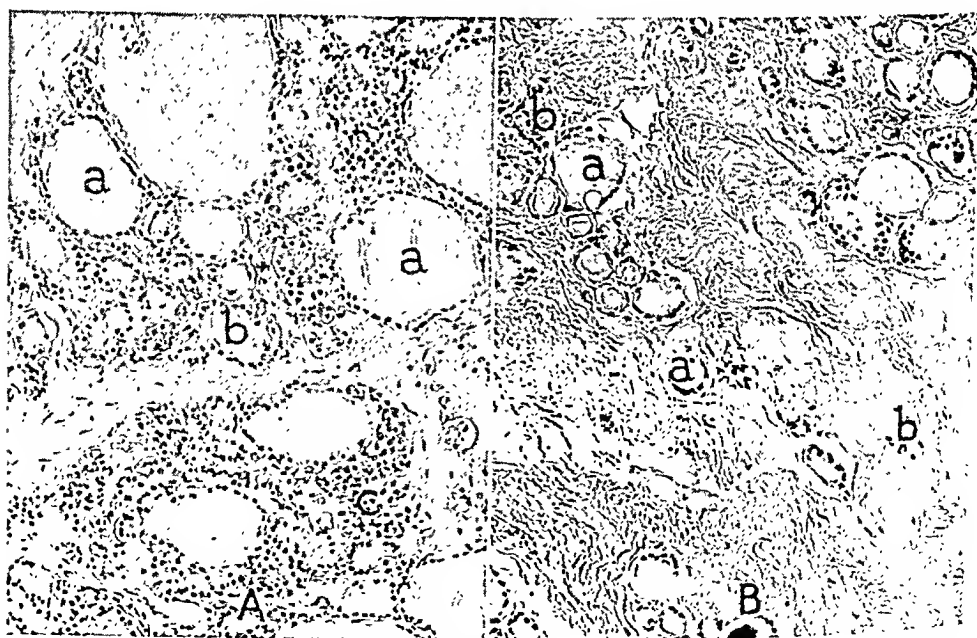
Fig. 7.—Thyroid of a patient aged 56: *A, a*, normal acini; *b*, small irregular acini, some with defective walls; *c*, cells diffusely distributed in the connective tissue. *B, a*, defective acini; *b*, cells irregularly placed.

are a measure of life expectancy. (Perhaps the insurance companies may ultimately demand an examination of the thyroid before issuing a policy.) These changes can be shown satisfactorily only in colored slides, but even in black and white pictures the differences may be indicated.

In the young adult the colloid stains a uniform deep pink with eosin. On the contrary, the senile gland is characterized by the gradual change in the colloid from acidophilic to basophilic. The cause or meaning of these changes has not been explained.

In the beginning these changes do not show with the usual laboratory stains but are evident with special stains. When senile changes
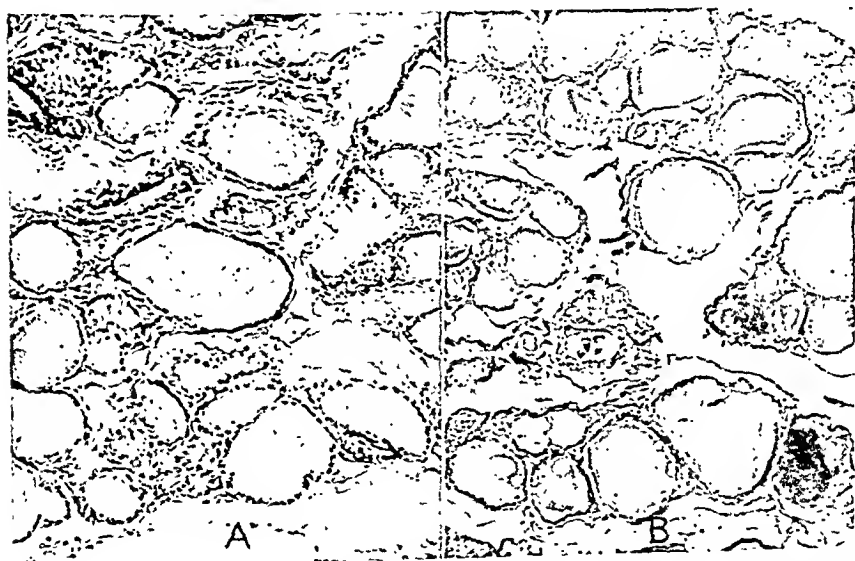
Fig. 8.—Thyroid of a patient aged 42: Biopsy specimen. *A*, hematoxylin-eosin stain. The colloid stains almost normally, with some vacuoles. *B*, tissue stained with Mallory's aniline blue. Many acini show the colloid deeply stained.

occur the colloid no longer stains with eosin but does stain with hematoxylin. With special dyes these changes may be demonstrated much earlier. For instance, the colloid of a gland may stain uniformly with eosin, while if Mallory's aniline blue stain is used some of the acini will take the orange G stain, shown as black in the photomicrograph (fig. 8).

Most slides show all these changes together. It must be repeated that the calendar is not a guide. I recently examined tissue from a man aged 79 which might well have belonged to a man in his prime. As a matter of fact, the thyroid of an aged person is not rarely a well preserved gland comparable with that of early adult life. Perhaps it is

this preservation of the gland that accounts for the fact that some persons become octogenarians.

The acinal cells suffer changes parallel with those in the colloid. Generally speaking, the greater the colloid changes the greater the change in the cells. At best the acinal cells are flat and endothelium-like. In advanced changes in the colloid the cells are absent. Those that are not there most certainly do not function; and since the change from complete absence to the flat cells usually found is so gradual, one is inclined to doubt the functional importance of the thin flat cells lining most of the acini which contain basophilic colloid.

COMMENT

A study of the thyroid glands of supposedly normal persons presents confusing variations. Many show changes parallel with those found in goiters from patients with goiter heart, that is, cardiac disease which disappears after removal of the goiter. Naturally these studies of the nongoitrous gland lead surgeons to ask themselves certain questions. What is the meaning of these changes in chemical reaction of the colloid in allegedly normal thyroids? No one knows, but it is known that these changes are found in goiters from patients with "goiter hearts" and that in such a patient the heart recovers when the goiter is completely removed. So much is incontrovertible. This well demonstrated clinical fact causes one to consider that possibly a degenerated thyroid gland, even though it has not acquired goitrous dimensions, may injure the heart. If this is true, the presence of a "goiter heart" demands the removal of the thyroid gland whether it is goitrous or not. First of all, one must recognize a "goiter heart" by clinical examination. It has been demonstrated to my satisfaction that, in the absence of a palpable goiter, if "goiter heart" is present the removal of the thyroid, enlarged or not, rids the patient of the cardiac disturbance. These observations must be multiplied a thousandfold.

This presents the original question: How big must a thyroid gland be in order to become cardiotoxic? The corollary is, what changes in the thyroid gland must be present before it can be declared the cause of the cardiac symptoms? This is easily decided if one follows the after-course. If the patient recovers from the cardiac signs one may conclude that the part removed was the cause. Multiply such an observation by thousands, and the conclusion is as accurate as one can hope to achieve. The patient, collectively speaking, is always right. If anatomic study does not corroborate clinical experience, one must extend the laboratory study. The surgeon should remember that when he sends a goiter to the laboratory he does so to secure not a diagnosis but an opinion.

This is the problem before surgeons today. Since it is now known that total removal of the .thyroid gland from the adult is a matter of indifference to the patient, it becomes merely a question of operative technic.

CONCLUSIONS

The tinctorial as well as the histologic study of the thyroid gland indicates the presence of certain changes which occur with advancing years. These changes parallel to some extent those associated with goiter associated with "goiter heart."

Physicians' knowledge of the relation of the nongoitrous gland to diseases of the heart is at present represented by a large question mark, but even this may presage an advance in understanding of the relation between the nongoitrous and the goitrous gland.

The similarity of structure suggests that the effect of the thyroid gland is a matter not of size but of function. One may determine the nature of this function by removing the gland and observing the results.

INTRACRANIAL HYPERTENSION OF UNKNOWN CAUSE

CEREBRAL EDEMA

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AND

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Occasionally one encounters a case which presents clinical symptoms and signs strongly indicative of a tumor of the brain, yet after complete studies one finds no evidence of neoplasm. The condition to be reviewed has been described in the literature under a number of different headings, none of which seems to be satisfactory. Terms such as "serous meningitis," "toxic hydrocephalus" and "pseudotumor" indicate the lack of knowledge regarding the exact nature of this condition.

There are a number of conditions which justly fall into the broad classification of pseudotumor of the brain. Dandy[1] listed and discussed the following: psychoneurosis, encephalitis, Schilder's disease, multiple sclerosis, syphilis, arteriosclerosis, hypertension, sinus thrombosis, various forms of meningitis (tuberculous, fungous and parasitic diseases), cerebral thrombosis and embolism, infantile cerebral palsies, hydrocephalus, macrocephalus, chondrodystrophy, oxycephalus, scaphocephalus and epilepsy.

Dandy classified the cases as those presenting papilledema with increased intracranial tension and those presenting papilledema without increased intracranial tension. He stated further that of all cases in which tumor of the brain is at first suspected, tumor will be subsequently eliminated in fully one-half.

The condition which we report and discuss in this paper is believed by us to be a definite disease syndrome. The patients present strikingly similar clinical and laboratory findings, and it is reasonable to suppose that the underlying pathologic condition in the brain is uniform and consistent in these cases.[2] It is felt that this disease should be

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1. Dandy, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 12, p. 449.

2. We regret that in our cases no material has been subjected to microscopic study, but we hope that opportunities will be afforded in the future for precise clarification of this point.

given consideration as a special entity or as a distinct category of pseudo-tumor, if from no other than a prognostic standpoint.

It is also believed that many of the cases of pseudotumor presenting papilledema and increased intracranial tension in which the patient progressed to complete recovery with no residual and in which the problem of the pathologic process remained unsolved belong to this group.[3] To such cases various pathologic possibilities have been ascribed but have not been proved to be present. We believe that we have eliminated by ventriculographic study the possibility of localized accumulations of fluid or other localized space-occupying masses. This is based on what one of us (O. H.) accepts as an axiom at the present time: Any localized, space-occupying mass of sufficient size and import to cause an increase in intracranial tension and papilledema will manifest its presence in a pneumoventriculogram.

In connection with the syndrome under discussion, a fairly consistent clinical picture appears in the headache and vomiting in association with papilledema and intracranial hypertension, occurring usually in young persons and terminating as a rule in marked improvement or complete recovery.

To the syndrome represented in this group of cases Quincke[4] in 1897 affixed the diagnosis of "serous meningitis," although other conditions were probably included in his report. The etiologic factors were considered to be influenza, overwork, injury to the head, alcoholism and otitis media.

In 1912, Warrington[5] described this syndrome under the heading of "serous effusions" and concluded that toxins are responsible for the production of excessive amounts of cerebrospinal fluid.

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3. After the reading of a paper by Wilder Penfield (The Principles of Physiology Involved in the Management of Increased Intracranial Pressure, Ann. Surg. **102**:548-554 [Oct.] 1935) the following discussion took place:

DR. WILLIAM J. MIXTER, Boston: I should like to ask Dr. Penfield why it is that a certain number of patients in the past who presumably had tumor of the brain, though this was never proved, were markedly relieved for a considerable period of time by subtemporal decompressions.

DR. WILDER PENFIELD, Montreal, Canada: I find it difficult to answer the question. I think there are a certain number of cases of pseudotumor, which are in reality not cases of tumor at all but cases of collection of subdural fluid, either secondary to trauma or secondary to some primary inflammatory process in one of the sinuses. I think in those instances there is a collection of fluid, high in protein, within the subdural space, which cannot escape. Consequently, decompression allows the fluid to drain into the muscles, and it does not reform, so that in some cases there have been permanent cures from decompression or trepanation.

4. Quincke, H.: Ueber Meningitis serosa und verwandte Zustände, Deutsche Ztschr. f. Nervenh. **9**:149-168, 1897.

5. Warrington, W. B.: Intracranial Serous Effusions of Inflammatory Origin, Quart. J. Med. **7**:93-117 (Jan.) 1914.

Passot [6] concluded that the condition is probably due to excessive cerebrospinal fluid in the subarachnoid space rather than in the ventricles.

Symonds [7] in 1931 reported 3 cases in which the condition followed otitis media and named the condition "otitic hydrocephalus."

Davidoff and Dyke [8] in 1936 reported 15 cases under the heading of "serous meningitis." In this series a history of otitis media was present in 4 cases, and a history of infection elsewhere in the body was obtainable in 2 other instances. The authors commented on the relatively large amount of fluid found in the subarachnoid space or on the "wet" appearance of the brain, as well as on the uniformly good prognosis which attended the condition once a correct diagnosis was made. Pneumoencephalograms taken of all of the patients except 2 showed the ventricles to be normal in size, shape and position. Autopsy on one of the patients, who died from another cause three months after discharge from the hospital, showed no evidence of inflammation of the brain. Questionable edema in the form of pericellular and perivascular spaces was observed.

McAlpine [9] designated the condition in his cases as "toxic hydrocephalus." He reported 5 examples in which nasopharyngeal infection seemed to be the cause.

Bailey [10] stated:

I believe that these obscure intracranial conditions result, in their chronic form, in the condition called by neurologists chronic serous meningitis and by neurosurgeons chronic arachnoiditis or pseudotumor. The cerebral affection is accompanied by a meningeal inflammation which results in some thickening and interferes with the proper circulation of the cerebrospinal fluid. . . . A sufficient number of necropsy reports exist to prove that such arachnoidal adhesions may be present when there is no tumor and I believe they are secondary to encephalitic affections, the nature of which is at present obscure. The primary disease may have been forgotten or have provoked such slight symptoms as to pass unperceived, while the secondary arachnoidal thickenings by compression of nervous structures or by impeding circulation of cerebrospinal fluid first attract the attention of the physician.

The symptoms of this disorder are those of intracranial hypertension without localizing phenomena. The problem, therefore, becomes identified at once with tumor of the brain in general and tumor of the posterior

6. Passot, R.: Méningites et états méningés aseptiques d'origine otique, Thesis, Paris, no. 247, 1913.

7. Symonds, C. P.: Otitic Hydrocephalus, Brain **54**:55-71 (April) 1931.

8. Davidoff, L. M., and Dyke, C. G.: A Presentation of a Series of Cases of Serous Meningitis, J. Nerv. & Ment. Dis. **83**:700-705 (Feb.) 1936.

9. McAlpine, D.: Toxic Hydrocephalus, Brain **60**:180-203 (June) 1937.

10. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

fossa in particular. The predominant symptom is headache, the onset of which is relatively acute. Vomiting consistently follows headache if the condition is severe. Occasionally somnolence and diplopia occur. Failure of vision may occur as the condition progresses, owing to choking of the disks. Convulsions occur rarely. Occasionally the patient complains of dizziness and unsteadiness. However, he is usually afebrile and appears surprisingly well in spite of definite signs of increased intracranial pressure. Papilledema is usually present. Ocular palsies, significant changes in the visual fields, nystagmus, ataxia and symptoms referable to the pyramidal tract rarely are present. Our cases have been typical in that there have been no definite localizing signs. The spinal fluid pressure is increased, but the constituents of the fluid are normal.

Pneumoencephalograms are indispensable for the exclusion of tumor of the brain. Once the nature of the condition is established, conservative management in the form of lumbar puncture and dehydration may be indicated. Subtemporal decompression will become the procedure of choice if more conservative measures are not effective in preventing failure of vision.

During the past two years, 5 examples of this disorder have come to our attention. In each case, at the time of the patient's admission to the hospital the tentative diagnosis was tumor of the brain, the history and clinical findings being not sufficiently clear to enable us to make a diagnosis with any great degree of certainty. Ventriculographic study was considered to be necessary before a proper diagnosis could be established and treatment instituted.

The patients ranged in age from 7 to 24 years. Three were females and 2 were males. Four of the patients gave histories of preceding or coincident infection as follows: 1 patient, mastoiditis, 1, cholecystitis and cholelithiasis, and 2, fever of undetermined origin. Complete recovery occurred in 3 patients. One patient had a moderate reduction of vision as a result of postpapillitic atrophy of the optic nerve. In another mild behavior difficulties seemed to be the only residual manifestation. Pneumoencephalograms were taken in each instance—4 ventriculograms and 1 encephalogram, the latter being made after ventriculographic study had been unsuccessful. The ventricular systems in the 5 patients were entirely normal.

REPORT OF CASES

CASE 1.—E. H., a white girl aged 7 years, was referred to the University Hospital by Dr. S. B. Chase, of Fort Dodge, Iowa, in March 1936.

History.—Shortly before Christmas 1935 the patient began to complain of severe headaches extending from the frontal to the occipital region. The head-

aches were frequently associated with nausea and vomiting, the latter being at times projectile, and there were several attacks of vertigo. She lost weight and strength.

About six weeks before examination she complained of severe earache on the right, associated with high fever, and was confined to bed for a week. The ear discharged some pus spontaneously, after which a diagnosis of mastoiditis was made and mastoidectomy was performed. The wound was completely healed eleven days prior to the child's admission to the hospital, but the headache was not relieved.

Other factors were: mild strabismus on one occasion, tinnitus at times, irritability on hearing noises, poor vision and peculiar mental episodes characterized by bizarre questions.

The past history of the patient and the family history were unessential.

Examination.—The child appeared pale and poorly nourished, cried easily and seemed below normal mentally.

The temperature was 98.6 F.; the pulse rate, 98; the respiratory rate, 22; the blood pressure, 100 systolic and 60 diastolic.

The tonsils were large and injected, and there were several large nodes in the right anterior triangle of the neck. The neck was not stiff, but the child complained of pain in the chest on bending the neck. The mastoid scar was well healed, and the ear drums did not appear abnormal.

The pupils and extraocular movements were normal. Vision was 6/8 and 6/10 in the right eye and the left eye, respectively. The visual fields were full. There was bilateral papilledema of 1 diopter, with many hemorrhages.

The child held her head somewhat tilted to the right when walking. The function of the seventh nerve seemed a little more active on the right than on the left. The tongue projected slightly to the right. Alternate movements of the tongue and hands were performed with abnormal slowness.

Laboratory tests showed: hemoglobin, 72 per cent; red blood cells, 3,650,000 per cubic millimeter and white blood cells, 8,350. The blood smear was normal. The Wassermann reaction of the spinal fluid was negative. Urinalysis gave negative results. Spinal puncture revealed a pressure of 200 mm. of water with the patient in the prone position. The fluid contained considerable globulin and 450 cells (bloody tap).

With the diagnosis of increased intracranial tension ("tumor syndrome") of unknown cause, a ventriculogram was taken. Twelve cubic centimeters of fluid was replaced with an equal amount of air. Both lateral ventricles and the third ventricle were well visualized and appeared normal in every respect (fig. 1).

Course.—Her condition changed little during the ensuing three weeks, but the spinal fluid at this time revealed a pressure of 480 mm. of water.

Subsequent to this she made steady improvement, complaining less and less of headache and vomiting only occasionally. After another two weeks the spinal fluid pressure was 170 mm. of water, and the papilledema had almost entirely subsided.

At the final check-up, made eight months after the first admission, the child appeared perfectly well. The fundi looked normal, and the disks did not appear atrophic. The spinal fluid pressure was 160 mm. of water. She was mentally clear and bright and had no complaints.

CASE 2.—G. W., a white boy aged 12, was referred to the University Hospital by Dr. A. Schultz of Fort Dodge, Iowa, in November 1936.

History.—Nine weeks previously this boy had "taken sick" and vomited. There was high fever, as well as some chilliness. He was thought to have "flu."

Although he felt ill, he was not drowsy and preferred to be up, because lying down increased his headache. He vomited a number of times after eating, but the vomiting was not projectile. The illness began with diarrhea, which later was replaced by constipation. Headache was constant and severe—"a pounding in the left parietal region and on top of the head." This was increased by noise and jarring.

About five weeks prior to examination he noticed double vision and also black specks before the eyes. Subsequently the vision became somewhat blurred. For the past four weeks his neck had been so stiff that he could hardly bend it. He had been rather active and not stuporous throughout the illness. The fever subsided about ten days after the onset, and he did not experience double vision at the time of examination. The headache and blurred vision, however, remained.

The family history was unessential.
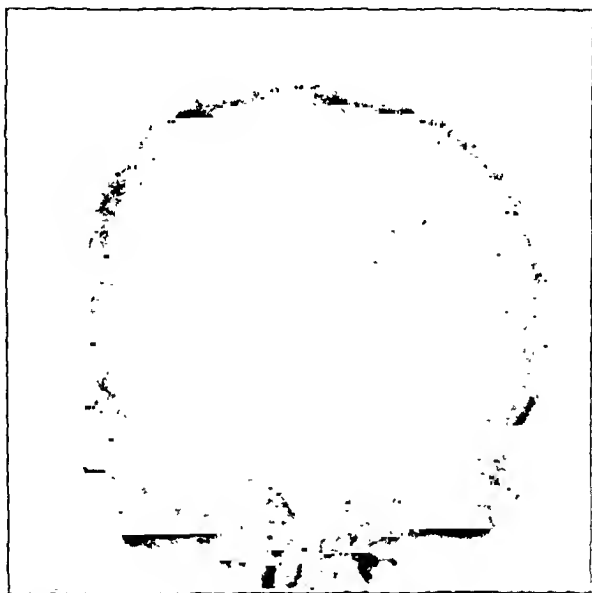
Fig. 1 (case 1).—Ventriculogram, anteroposterior view.

He was thought to have had scarlet fever in early childhood. Two years prior to examination there had been a slight injury to the head without unconsciousness. A tonsillectomy had been done five months previous to examination.

Examination.—General physical examination gave negative results throughout. The temperature was 98.6 F.; the pulse rate, 95, and the respiratory rate, 30. The blood pressure on admission was 110 systolic and 65 diastolic.

Neurologic examination revealed bilateral papilledema of 3 diopters. The retinal veins were dilated, and a few small hemorrhages were present. Vision was 6/6 in each eye, and the visual fields were normal save for large blind-spots. The extraocular movements were normally performed. Otherwise the neurologic examination gave essentially negative results.

Laboratory tests showed the blood and urine to be normal. The Wassermann reaction was negative. The spinal fluid pressure was 200 mm. of water with the

patient in the prone position and rose rapidly to 325 on compression of both external jugular veins. The fluid showed a trace of globulin, 34 mg. of protein and 78 mg. of sugar per hundred cubic centimeters, and 9 lymphocytes per cubic millimeter.

With the diagnosis of increased intracranial pressure ("tumor syndrome") of unknown cause a ventriculogram was taken. Only 10 cc. of fluid was obtained, this being replaced with an equal amount of air. The ventriculograms showed normal conditions. The ventricular system appeared, perhaps, a little smaller than normal (fig. 2).

Treatment.—Treatment consisted in moderate limitation of fluid intake and daily spinal punctures for twelve days, after which time the pressure was reduced to about 60 mm. of water with the patient in the prone position.

Course.—The choked disks were definitely receding and the headaches abating when the boy was discharged, at the end of one month.

About two weeks after returning home he had a mild recrudescence of the original illness, consisting of a chill and fever associated with intermittent head-
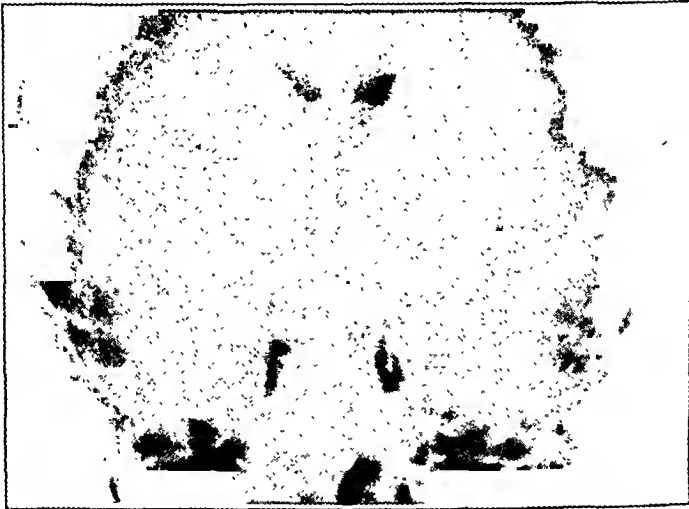
Fig. 2 (case 2).—Ventriculogram, anteroposterior view. The angles of the lateral ventricles are sharp, and the ventricles are small.

ache. His appetite remained good, but he vomited on one occasion. At this time he complained of shooting and stabbing pains in both thighs.

The check-up revealed that the disks had receded to about 1 diopter, though the spinal fluid pressure was 220 mm. of water. He was discharged after a short stay in the hospital, and on a check-up made in June 1937, seven months after his original illness, he was found to be feeling well and was free from headaches. The eyegrounds showed complete recession of the papilledema, with only a slightly fuzzy appearance of the disk margins. A spinal puncture was not made at this time, but it was felt that the patient had made a full recovery.

CASE 3.—E. F., a white boy aged 12, was referred to the University Hospital in November 1936, by Dr. George Stevenson of Cedar Rapids, Iowa.

History.—Six months prior to his admission to the hospital the patient began to complain of severe frontal headache, present day and night and aggravated by walking and jarring. He slept excessively. Two months later he became dizzy,

at which time a physician stated that the temperature was elevated and that the optic disks were choked. Two months before admission he noticed a swelling under the left jaw. This condition seemed to aggravate the headache. Several projectile emeses occurred at this time.

The family history and the past history of the patient were unimportant.

Examination.—The boy appeared lethargic. The temperature was 98.4 F.; the pulse rate, 66 and the respiratory rate, 16. The blood pressure was 108 systolic and 69 diastolic. General physical examination showed normal conditions except for moderate enlargement of the submaxillary lymph nodes.

Neurologic examination revealed that the pupils reacted well to light and came down well on accommodation. Nystagmoid jerks were elicited on deviation of the eyes to the right and left. There was no strabismus. The fundi were
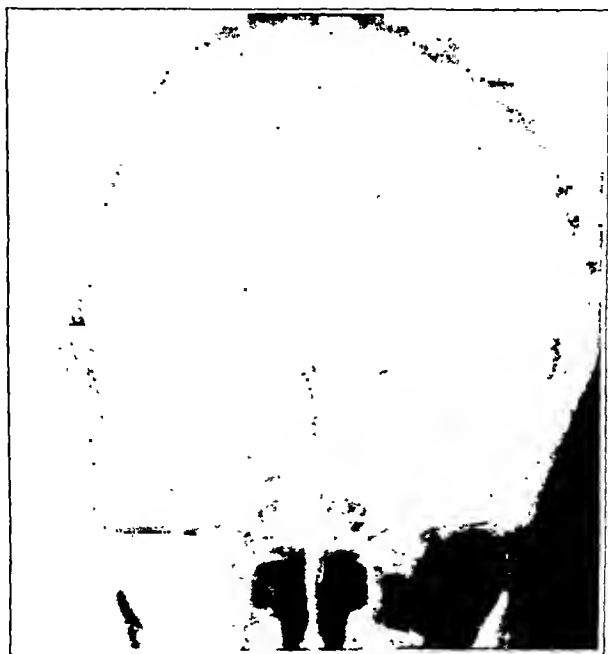
Fig. 3 (case 3).—Ventriculogram, anteroposterior view, taken after spinal injection of air. The defect of the skull is an artefact.

normal. The other cranial nerves were intact. The neck was not stiff. The strength of the extremities, the reflexes and the sensory responses were normal.

Laboratory studies showed a normal blood count and normal urine. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid was under an initial pressure of 24 mm. of mercury (326 mm. of water) with the patient in the prone position. The spinal fluid was clear. The Pandy test for globulin gave a negative result. There was 1 lymphocyte per cubic millimeter. The Wassermann reaction of the spinal fluid was negative.

The tentative diagnosis was tumor of the posterior fossa.

Ventriculographic study was unsuccessful. Encephalograms were satisfactory, revealing an entirely normal ventricular system (fig. 3).

Course.—Improvement was gradual. At examination in March 1937, five months later, the boy was entirely normal.

The final diagnosis was encephalitis.

CASE 4.—J. H., a white woman aged 24, was referred to the University Hospital in January 1937, by Dr. F. E. Simerel of Brooklyn, Iowa.

History.—About four months previous to admission the patient began having headaches. These were more frequent and more severe in the evening, gradually increasing in severity. The headache would commonly start over the eyes and radiate to the occiput. Vomiting occurred only once. Three months prior to admission vision became blurred in the left eye, and there was also double vision. The left eye became almost blind in two months. Vision in the right eye became somewhat blurred also.

Fig. 4 (case 4).—Ventriculogram, anteroposterior view. The apparent vertical elongation of the system is due to the angle at which the x-ray tube was placed with respect to the head.

During the early course of the illness there had been a mild fever, the temperature being from 99 to 100 F., but no chills. At the time the vision first began to blur, the left side of the face swelled, and the left eye became puffy. There were cramps in the neck and back, and the neck was stiff.

This patient had previously been admitted to the University Hospital, July 1935. The history and the results of examination were typical of disease of the gallbladder and the Graham-Cole test revealed a nonfunctioning gallbladder. Cholecystectomy, choledochostomy and appendectomy were done, two stones being removed from the common duct. She was discharged improved on the twenty-ninth postoperative day, the T tube having been removed from the common duct.

She had also been subject to frequent sore throats, and on her return to the hospital in November 1935 the tonsils were removed.

Examination.—The patient was obese; otherwise the general examination showed her to be essentially normal.

The pupils and ocular rotations were normal except that convergence of the right eye was poorly performed. Visual acuity was 6/21 in each eye. Both eyegrounds revealed old choking, with some postpapillitic atrophy and stellate retinitis. Both visual fields were irregularly constricted, and the blindspots were enlarged. Otherwise the neurologic examination gave negative results.

A roentgenogram of the skull revealed nothing unusual.

Laboratory studies of the blood and urine disclosed no abnormality. The Wassermann reaction of the blood was negative. The dextrose tolerance curve was not unusual. The spinal fluid was under a pressure of 170 mm. of water with the patient in the prone position. It rose and fell normally on compression of the jugular veins. The cell content was normal. There was a trace of globulin. The protein content was 46 mg. and the sugar content 86 mg. per hundred cubic centimeters.

A ventriculogram was made, which revealed that the lateral ventricles and the third ventricle were of normal size. *The ventricular system was normal in every respect, with good visualization of the third ventricle* (fig. 4).
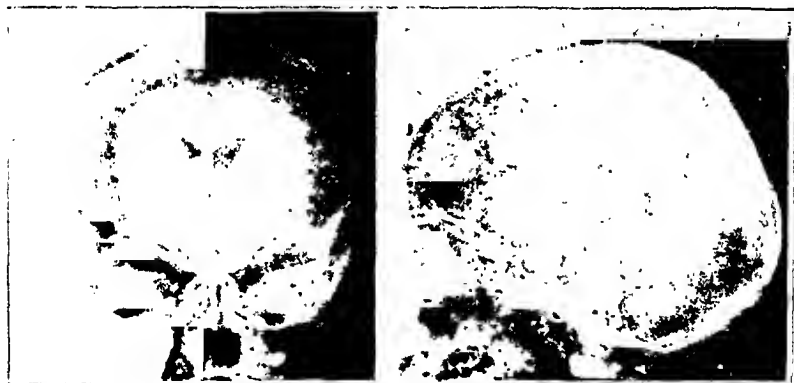
Fig. 5 (case 5).—Ventriculogram, anteroposterior and right lateral views.

Course.—The patient was discharged. Five months later she returned to the hospital. The headaches had gradually lessened until she was almost entirely free from them. She no longer complained of double vision, and the visual acuity had improved, being 6/15 in each eye. The visual fields showed some widening as compared with the findings on the previous admission. The papilledema had almost entirely receded, and there was evidence of moderate postpapillitic atrophy. Otherwise the general and neurologic examinations gave negative results. It was evident that she had made considerable spontaneous improvement.

CASE 5.—R. S., a white girl aged 12, was referred to the University Hospital in August 1937, by Dr. J. M. Fettes of Spencer, Iowa.

History.—About two weeks previously, without apparent cause, she had begun to have headache referred to the forehead and behind the eyes. It was present most of the time but worse in the evening. She had vomited several times, the vomiting being projectile. Acetylsalicylic acid gave some relief.

For the past one and a half weeks she had remained in bed. She had been drowsy and had slept most of the time.

Recently the headache had been located in the back of the head. The vision had become blurred, and at the time of examination she "saw double," because of which she kept one eye closed. She complained of ringing in the ears.

The family history and the past history of the patient were unessential except that the patient had had frequent attacks of sore throat.

Examination.—The patient lay on a cart with the eyes closed. She appeared ill and was drowsy but could be aroused without difficulty. The temperature was 100 F.; the pulse rate, 68; the respiratory rate, 18; and the blood pressure, 108 systolic and 70 diastolic. Otherwise the general examination gave essentially negative results.

Neurologic examination gave the following significant findings: The pupils and ocular rotations were normal. Visual acuity was 6/9 in the right eye and 6/18 in the left. The visual fields were moderately constricted and the blind spots enlarged. The eyegrounds revealed papilledema of about 3 diopters. The retinal veins were engorged and tortuous. Audition was normal. The results of caloric tests were normal. The neck was rigid and painful on movement. The Kernig sign was present to a moderate degree on both sides. Alternate movements were performed with abnormal slowness on both sides. When standing with heels together and eyes closed, the girl tended to fall backward. Her gait was slow and careful, and she veered to the right.

Laboratory studies showed the blood and urine to be normal. The Wassermann reaction of the blood was negative. A spinal puncture revealed a spinal fluid pressure of 370 mm. of water with the patient in the prone position. The fluid gave a positive reaction to the test for globulin and contained 1 lymphocyte per cubic millimeter. The Wassermann reaction was negative.

The impression was that of a subtentorial tumor, but a ventriculogram showed the lateral ventricles and the third ventricle to be normal in every respect (fig. 5).

Course.—The patient improved under conservative management, so that two weeks after admission she was mentally alert and cheerful and did not complain of headache. At this time a spinal puncture revealed a pressure of 70 mm. of water, with normal rise and fall when pressure was applied to and released from the jugular veins. The fluid gave a positive reaction to the test for globulin. It contained 38 mg. of protein per hundred cubic centimeters and 15 lymphocytes per cubic millimeter.

The papilledema appeared to be receding. The patient was discharged with a diagnosis of encephalitis.

COMMENT

The cases reported here, while a small series, nevertheless present a clinical syndrome of intracranial pathologic disturbance which has certain definite characteristics. The literature is not devoid of similar case reports.

The important characteristic feature of these cases is the unexplained intracranial hypertension. The history may or may not disclose a concomitant or preceding infection or systemic disease. The condition appears to be largely a disease of youth, the patients coming to the physician because of relentless headache. The signs found on examination can be attributed principally to increased intracranial tension and are characteristically papilledema and high pressure of the spinal fluid.

Outstanding complaints in this series of cases were irritability, somnolence and headache that was made worse by the slightest jarring. Stiffness of the neck was definite in 4 instances.

The protein, sugar and cell contents of the spinal fluid were within normal limits. A trace of globulin was elicited in 2 cases.

From this series it would seem that if there are chills and fever during the course of the illness they are related to the systemic infection rather than to the intracranial condition primarily.

Inasmuch as the patient presents symptoms of a tumor of the brain without localizing signs, a ventriculogram is indispensable to correct diagnosis. The normal ventriculographic picture rules out neoplasm.

One of us (O. H.) has never encountered a tumor of the brain associated with increased intracranial tension that was not also accompanied by evidence of dilatation, distortion or filling defect of the ventricles.

Recovery occurs over a period of several months to a year or so, with no neurologic residuals except postpapillitic atrophy of a degree depending on the severity and duration of choking of the disks.

Whether repeated spinal punctures or artificial dehydration measures hasten recovery is difficult to say. Concerning our cases, in retrospect, we do not believe that surgical decompression would have been of sufficient added advantage to warrant the procedure. The process was undoubtedly subsiding in the patient in case 3 at the time of her admission to the hospital. It was felt that little could have been gained by decompression. It is possible, however, that certain patients will require this procedure because of rapidly advancing visual loss.

In fact, little active treatment of any kind was administered to any of these patients except one. Most of the recovery occurred at home.

A rational rule of therapy might be as follows: The diagnosis having been established and it having been ascertained that the spinal fluid pressure is 250 mm. of water or more with the patient in the prone position, daily spinal punctures and dehydration measures are in order. The papilledema should be carefully followed. If this progresses objectively and there is evidence of diminishing visual acuity in spite of conservative measures, subtemporal decompression may be justified. It is reasonable to expect operative decompression to relieve the patient subjectively and to prevent additional damage to the optic nerves.

As our cases indicate, however, decompression is not always necessary for an excellent outcome.

On the other hand, the symptoms of this disease, unlike those of hydrocephalus, are materially alleviated by subtemporal decompression.

The hypothesis that some interference with the absorption of cerebrospinal fluid is the cause of increased intracranial tension appears to be almost universally accepted.

The one outstanding fact which disproves this idea is the absence of dilatation of the ventricles. In fact, the ventricular system may seem smaller than usual, regardless of when the ventriculogram is made during the course of the illness. This same impression was gained by Davidoff and Dyke.[8]

The one definite fact which has been elicited from the cases here reported is that the disease is not hydrocephalus. Additional cases reported in the literature in which pneumograms were made reveal the same findings. In the light of our understanding of cerebrospinal fluid circulation and obstructive hydrocephalus, any reduction in the absorption of cerebrospinal fluid here could hardly be acceptable.[11] Consequently, any diagnostic term incorporating hydrocephalus would appear to be wrongly applied.

If this assumption is correct—that decreased absorption of cerebrospinal fluid is not the fault—only one other cause can remain, and that is swelling or edema of the brain.

A "wet" brain, with particular reference to increased depth of the subarachnoid spaces, has been described in the literature. On making trephine openings preparatory to ventricular puncture, one of us (O. H.) was not impressed with this condition in the cases reported here, although only a limited area of the cortex was examined. In reviewing his own experience, he does not find that he ever encountered a wet, cystic appearance of the subarachnoid spaces except where some degree of cerebral atrophy had occurred.

Davidoff, however, encountered this condition in 13 of his 15 cases in which surgical decompression was done. It is not unreasonable to suppose that edema of the subarachnoid space might be a part of a generalized extracellular and interstitial edema without interfering materially with normal circulation of the cerebrospinal fluid.

The same evidence that speaks for the improbability of decreased absorption of cerebrospinal fluid as a cause of intracranial hypertension speaks against excessive production of cerebrospinal fluid as a cause.

It is evident in the present group of cases that the pathologic process was not severe enough to cause destruction of brain tissue. The evi-

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11. We have encountered another condition (malignant hypertension) which, when associated with increased intracranial tension is also associated with a normal or smaller than normal ventricular system. A postmortem examination in such a case revealed changes in the cerebral vessels, edema of the white matter and hemorrhage. Evidently the increased tension in this condition is due to cerebral edema and not to obstruction of the circulation of the cerebrospinal fluid.

We have also made encephalograms in a few cases of meningitis (in 1 instance, tuberculous) and have reviewed encephalograms in such cases made by the department of pediatrics. In every instance the ventricles have been dilated and the sharp angles in the ventriculographic shadows rounded. In such cases the increased tension is largely contributed to by interference with absorption of cerebrospinal fluid, as a result of which the ventricles become dilated.

dence of this is the fact that there is no neurologic residual and the fact that the ventriculograms did not indicate atrophic changes. The time which had elapsed between the onset of the disease and the taking of ventriculograms in 4 of the cases was sufficient to have enabled one to demonstrate atrophic changes if the disease had been destructive. The interval between the onset of disease and the ventriculographic examination in each of the five cases was two and one-half months, nine weeks, six months, two and one-half months and two weeks, respectively.

That the white matter can undergo tremendous swelling from a number of causes (tumor, infection, trauma) is common knowledge. Intracellular edema with demonstrable swelling of the oligodendroglia may be an important factor.[12] This type of edema is prolonged and is probably unrelieved directly by spinal fluid drainage.

We believe that this is the pathologic process underlying the syndrome in the cases reported here and that it develops as a reaction to toxins—a sterile process. The fact that it is not an inflammatory process in the true sense is evidenced by the absence of an abnormal number of leukocytes and of increase in the protein of the spinal fluid. The edema is probably evolved in a relatively short period but subsides slowly.

For this particular group of cases, we believe cerebral edema would be a more fitting diagnosis than any which has as yet been proposed.

We believe that it is equally important that this syndrome be not confused with, or diagnosed as, encephalitis. This syndrome differs from encephalitis in three significant ways: 1. Encephalitis is commonly characterized by convulsions. Convulsions have not occurred in this syndrome. 2. In encephalitis the spinal fluid demonstrates cytologic and chemical evidence of inflammation, while in this syndrome the constituents of the fluid are strikingly normal. 3. Encephalitis is commonly followed by neurologic residuals. Ventriculographic evidence of cerebral destruction and atrophy is repeatedly obtainable. The reverse is true of this syndrome.

CONCLUSIONS

1. A syndrome variously referred to as "pseudotumor," "serous meningitis" and "otitic hydrocephalus," 5 cases of which are here reported, is probably due to cerebral edema, extracellular, intracellular or both.

2. Cerebrospinal fluid that appears consistently normal from cytologic and chemical standpoints excludes an inflammatory process of the cerebrum or meninges.

12. Penfield, W.: A Further Modification of Del Rio Hortega's Method of Staining Oligodendroglia, Am. J. Path. **6**:445-447 (July) 1930. Penfield, W., and Cone, W.: Acute Swelling of Oligodendroglia: A Specific Type of Neuroglia Change, Arch. Neurol. & Psychiat. **16**:131-153 (Aug.) 1926.

3. Absence of the slightest evidence of ventricular dilatation at any time during the disease excludes the possibility that decreased absorption or excessive production of cerebrospinal fluid is the cause of the increased tension.   Likewise, this finding demonstrates that cerebral atrophy does not occur and hence that the pathologic process is not destructive (except for the atrophy which may follow prolonged papilledema).

4. For the present, cerebral edema would be the most fitting diagnosis for this type of pseudotumor.

5. Recovery is spontaneous (requiring a period of months) and occurs even when no decompressive therapy is administered.

SWELLING OF THE BRAIN IN CASES OF INJURY TO THE HEAD

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Dehydration methods in the treatment of injury to the head have refocused attention on the subject of the water content of the brain and the partition of fluids within the cranial cavity. The total volume of the cranial content is fixed by the rigid confines of the bony cranial walls (Monroe-Kellie Doctrine).[1] To maintain pressure equilibrium, a change in one component should be associated with a reciprocal change in some other.[2] The components involved are brain tissue, cerebral fluid and blood. The major factor is brain tissue, the chief subdivisions of which are solid matter (which is constant), intercellular water, intracellular water and parenchymatous hemorrhages. The cerebral fluid is divided into the subarachnoid and ventricular parts.[3] The extraparenchymatous blood includes that within the vessels outside the brain as well as that extravasated as subarachnoid, subdural or extradural hemorrhage.[4]

It has long been taught that with trauma to the head there are an increase in quantity of cerebral fluid and a swelling of the brain substance by edema.[5] These increases would induce a corresponding decrease in blood content of the brain and would lead eventually to

1. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injections of Various Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919. Page, I.: Chemistry of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. Reichardt, M.: Ueber die Untersuchung des gesunden und kranken Gehirnes mittels der Wage, Jena, Gustav Fischer, 1906.

3. Jackson, H.: The Circulation of the Cerebrospinal Fluid, J. A. M. A. **79**:1394 (Oct. 21) 1922.

4. Jackson, H.: Head Injuries, Practitioner **138**:188, 1937.

5. (a) Werden, D. H.: Drainage of Cerebrospinal Fluid in the Treatment of Acute Head Injuries, Arch. Surg. **34**:424 (March) 1937. (b) Häussler, G.: Hirndruck—Hirnödem—Hirnschwellung, Zentralbl. f. Neurochir. **2**:247, 1937. (c) Wilson, F., and Gorrell, R.: Traumatic Edema with Skull Fracture, Nebraska M. J. **21**:95, 1936. (d) Craig, W. M.: Physiology, Pathology and Treatment of Craniocerebral Injuries, New England J. Med. **212**:77, 1935.

serious cerebral anemia.[6] The increased quantity of cerebral fluid has been attributed to irritation by extravasated blood [7] or to decreased absorption. The cerebral edema has been attributed to compression of fluids out of the capillaries, to vasomotor paralysis, to anemia and osmotic changes and to accumulation of acid because of the anemia.[8]

The doctrine of an increased quantity of cerebral fluid after trauma to the head is based partly on the increased cerebrospinal fluid pressure commonly found. An increase in pressure does not necessarily imply an increase in quantity. A swollen brain pressing on the same quantity or even on a smaller quantity of cerebral fluid can produce an increase in pressure. An actual increase in quantity has been attested.[5a] In some cases of head trauma there is no increase in either pressure or quantity of cerebrospinal fluid. While it is conceded that there may be no increase in subarachnoid fluid, other observers emphasize the increase in ventricular fluid.[9] Internal traumatic hydrocephalus is frequently referred to in the foreign literature as an important feature of the surgical pathologic picture presented by head trauma. These considerations have led to the therapeutic principle of lumbar puncture and drainage in cases in which increased cerebrospinal fluid pressure is found.[10] Whether or not the actual quantity of fluid is increased, lumbar puncture will still reduce pressure. The removal of only a small quantity (as little as 14 cc.) may be enough to restore the pressure to normal. To combat the internal hydrocephalus, ventricular drainage has been suggested.[11]

The current tendency, despite considerable disagreement, is to regard the swelling of the cerebral tissue in the absence of gross hemorrhage as the principal compressing factor in head injuries. On the principle that the cerebral swelling is a cerebral edema, an increase in intra-

6. Lehman, E., and Parker, W.: The Unsolved Problems of Brain Injury, Internat. Clin. **3**:181, 1935.

7. Weed, L. H.: Forces Concerned in Absorption of Cerebrospinal Fluid, Am. J. Physiol. **114**:40, 1935.

8. Pilcher, C.: Experimental Cerebral Trauma: The Fluid Content of the Brain After Trauma of the Head, Arch. Surg. **35**:512 (Sept.) 1937. Jorns, G.: Hirnödem und Hirnschwellung, Chirurg **8**:437, 1936.

9. Arnand, M.: Recherches sur les hypertension intracraniennes bloquées du liquide céphalo-rachidien consécutives aux traumatismes craniens, et en particulier sur les hypertensions intraventriculaires, Bull. et mém. Soc. nat. de chir. **59**:843, 1933. Hauptmann: Die Objektivierung postcommotioneller Beschwerden durch das Encephalogram, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:846, 1927.

10. Munro, D.: The Therapeutic Value of Lumbar Puncture in the Treatment of Cranial and Intracranial Injury, Boston M. & S. J. **193**:1187, 1925. Jackson, H.: The Management of Acute Cranial Injuries by the Early Exact Determination of Intracranial Pressure and Its Relief by Lumbar Drainage, Surg., Gynec. & Obst. **34**:494, 1922.

11. Denis, R.: Au sujet du traitement des lésions traumatiques cranio-encéphaliques, J. de chir. **42**:873, 1933.

parenchymatous fluid, dehydration methods have been widely used in treating such injuries.[12] By restricting fluid intake and inducing catharsis, Fay sought to decrease the production of cerebrospinal fluid and to diminish the water content of the brain tissue.[13] The intravenous injection of hypertonic dextrose also extracted water from the tissues.[14] It was found, however, that after producing a brief salutary effect part of the dextrose migrated into the tissues.[15] The dextrose in the blood stream was excreted. The osmotic relation was reversed. Water flowed back into all the tissues, including the brain. The cerebrospinal fluid pressure suffered a secondary rise, and, in addition, shock was favored by reduction in general blood volume.[16] Sucrose solutions administered intravenously have apparently corrected these difficulties because the sucrose molecule does not migrate into the tissues.[17] It has been established clinically and experimentally that a general dehydration diuresis occurs, and there is a fall in cerebrospinal fluid pressure, with no secondary rise and no vascular shock. Occasional reports of nephritis following injections of sucrose and the possible harmful effects of too rapid or too violent dehydration of brain tissue discourage the unrestricted use of this agent.[18]

12. Weed, L. H., and Hughson, W.: Systemic Effects of the Intravenous Injection of Solutions of Various Concentrations, with Special Reference to the Cerebro-Spinal Fluid, Am. J. Physiol. **58**:53, 1921.

13. Fay, T.: The Treatment of Acute and Chronic Cases of Cerebral Trauma by Methods of Dehydration, Ann. Surg. **101**:76, 1935.

14. Sachs, E.: Treatment of Head Injuries, Internat. J. Med. & Surg. **46**:567, 1933; The Diagnosis and Treatment of Head Injuries, J. A. M. A. **81**:2159 (Dec. 29) 1923. Jackson, H.; Kutsunai, T.; Leader, L. O., and Joseph, L. D.: Effect of Hypertonic Dextrose Solutions on Intracranial Pressure in Acute Cranial Injuries, ibid. **100**:731 (March 11) 1933.

15. Gregersen, M., and Wright, L.: The Effect of Intravenous Injection of Sucrose and Glucose upon the Reducing Power of Cerebro-Spinal Fluid, Before and After Hydrolysis, Am. J. Physiol. **112**:97, 1935.

16. Milles, G., and Hurwitz, P.: Effect of Hypertonic Solutions on the Cerebrospinal Fluid Pressure, with Special Reference to Secondary Rise and Toxicity, Arch. Surg. **24**:591 (April) 1932.

17. Hahn, E. V.; Ramsey, F. B., and Kohlstaedt, K. G.: Clinical Experience in the Use of Sucrose Instead of Dextrose in the Osmotic Therapy of Increased Intracranial Pressure Occurring in Cases of Acute Brain Injury, J. A. M. A. **108**:773 (March 6) 1937. Jackson, H.; Dickerson, D., and Gunther, A.: The Reduction of Intracranial Pressure in Cerebral Injury by the Intravenous Use of Hypertonic Sucrose Solutions, Ann. Surg. **106**:161, 1937. Bullock, L.; Gregersen, M., and Kinney, R.: The Use of Hypertonic Sucrose Solution Intravenously to Reduce Cerebro-Spinal Fluid Pressure Without a Secondary Rise, Am. J. Physiol. **112**:82, 1935.

18. Masserman, J.: Intracranial Hydrodynamics: Central Nervous System Shock and Edema Following Rapid Fluid Decompression of the Ventriculo-Subarachnoid Spaces, J. Nerv. & Ment. Dis. **80**:138, 1934. Russell, W. R.: Cerebral Involvement in Head Injury, Brain **55**:549, 1932. Barker, H.: Dangers of Rapid Diuresis, Illinois M. J. **72**:313, 1937.

That the brain in the presence of trauma to the head is enlarged and swollen cannot be questioned.[19]　The brain in such a condition, according to the estimate of the coroner's physician, Dr. J. Kearns, averages 30 to 50 Gm. more in weight than the normal brain of a person of the same age and weight.　That the cerebrospinal fluid pressure is often increased in cases of trauma to the head is undenied.　Clinical studies, however, leave many undecided factors, such as the quantity and distribution of the cerebrospinal fluid and the nature of the swelling of the brain.　These unknown factors hamper analysis.　The following studies were undertaken in order to determine by actual measurement at the autopsy table just how much fluid there is in and about the brain in cases of head trauma and to trace, if possible, the mechanism of the cerebral enlargement.　It is recognized that this material represents only end stages in the traumatic process.　Yet *mortui vivos docent*.　From these end stages physicians should be able to look backward and learn something definite about the pathogenesis of intracranial compression or at least clear the way for more detailed analysis of the mechanisms involved by the more easily controlled experimental method.

There are but few autopsic reports in sufficient detail to permit analysis of the mechanism of swelling of the brain.[20]　Small sample methods of determining the water content of the traumatized brain [21] are open to the serious objection that minute variations in the proportions of gray and white matter in the specimens will give greater differences in total water content of the samples than will the trauma itself.[8]　Gray matter contains 12 per cent more water than does white matter.　In the whole brain there is 57 per cent gray matter and 43 per cent white.　Small (10 to 15 Gm.) samples taken from the same area of the brain but differing slightly in the proportion of gray and white matter were found to vary up to 4 per cent in water content.　The report, therefore, based on this method, that the brain of a traumatized head contains from 0 to 2.2 per cent more water than does the normal brain cannot be accepted without reservation.[8]

OBSERVATIONS

The amount of cerebrospinal or extraparenchymatous fluid was first determined.　In normal brains the total amount of fluid which could be collected at autopsy varied between 30 and 60 cc.　This

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19. LeCount, E. R., and Apfelbach, C. W.: Pathologic Anatomy of Traumatic Fractures of the Cranial Bones and Concomitant Brain Injuries, J. A. M. A. **74:** 501 (Feb. 21) 1920.

20. Courtney, J. W.: Traumatic Cerebral Edema, Boston M. & S. J. **140:** 345, 1899. Reichardt, M.: Bericht über Folgen der Hernverletzungen, Berl. klin. Wchnschr. **55:**822, 1918. LeCount and Apfelbach.[19]

21. Apfelbach, C. W.: Traumatic Fractures of the Cranial Bones: I. Edema of the Brain; II. Bruises of the Brain, Arch. Surg. 4:434 (March) 1922.

included the fluid in the subarachnoid spaces of the brain and spinal
cord as well as the few cubic centimeters which was found at the
bottom of the otherwise empty ventricles. This quantity is less than
the 100 to 150 cc. usually given as the normal quantity during life.
There may be some agonal or postmortem absorption of fluid, but
this factor would probably hold for the definitive as well as the control
cases and, in fact, did not vary appreciably with the interval before
autopsy, with the terminal temperature or with the cause of death. In
patients with alcoholic "wet brain" or in those who died of congestive
heart failure or renal failure there was an abundance of cerebrospinal
fluid at autopsy (up to 150 to 160 cc.). The sulci were rounded and
atrophied.[22]

The brains of traumatized heads showed a disappointing meager-
ness of fluid in the subarachnoid spaces. In fatal cases we had expected
to observe an. increased quantity of fluid. Actually, we observed at
the autopsy table hardly enough fluid to measure. While there were
some exceptions, 5, 10 or 15 cc. was usually as much as could be col-
lected. This was observed mostly in the basal cisterns and in the
spinal subarachnoid spaces. Often the cerebral subarachnoid spaces
were so dry that there was not even the few drops necessary to main-
tain the normal luster of the pia mater. The dryness of the subarachnoid
spaces after trauma to the head has been described by LeCount. The
sulci of the brain were obliterated and the convolutions flattened.

The lateral ventricles, however, were dilated to almost twice the
normal size. They were filled with 30 to 60 cc. of fluid which did not
run freely into the subarachnoid spaces when the brains were removed.
This internal traumatic hydrocephalus has been frequently described,
especially in the French literature. It could have squeezed the sub-
arachnoid spaces dry. It could account at least in part for the enlarge-
ment of the brain.

To hunt further for the cause of the increased weight of the brain
in cases of trauma to the head, the intraparenchymatous water content
of a group of brains from traumatized heads and of a group of normal
brains was determined by dehydration to a dry residue of constant
weight. Large samples, comprising roughly an entire cerebral hemi-
sphere and weighing over 400 Gm., were used. This eliminated the
error inherent in the small whole sample method or the error in an
insufficiently skilful separation of gray and white matter. Several
methods of dehydration were used.

In calcium chloride or sulfuric acid desiccators the normal brain
was reduced to constant weight in six weeks and showed a water

22. Roberson, R. S.: Cerebral Edema in Chronic Alcoholism (Alcholic Wet
Brain), South. Med. & Surg. **94**:584, 1932.

content of 78.1 per cent.[23] The "alcoholic," or "wet," brain was truly wet, showing after six weeks a water content of 81.6 per cent.[24] The brains from traumatized heads retained water more tenaciously, being finally reduced to constant weight only after three months, and then showed a water loss less than that of the alcoholic wet brain and even less than that of the normal brain. The loss of water from the 3 brains from traumatized heads was 75.7, 75.1 and 74.2 per cent respectively (table 1). These brains were thus even dryer than normal.[25]

It cannot be stated that at the end of the experiment the brain substance was completely dehyrated by this method. Complete dehydration is interfered with by the fat content of the brain. The brain substance was reduced to apparently dry but resin-like small particles which may

TABLE 1.—*Dehydration of Brain Substance by Calcium Chloride Desiccator*

Case No.	Condition of Brain	Hours After Death	Patient			Subarachnoid Fluid, Cc.	Ventricular Fluid, Cc.	Weight of Brain, Gm.	Survival After Admission	Terminal Temperature, F.	Treatment	Percentage of Water in Brain
			Age	Weight, Lb.	Height							
1	Trauma	15	38	150 (68 Kg.)	5′ 8″	10	50	1,536	2 days	104.8	200 cc. 50% sucrose; lumbar puncture	75.7
2	Trauma	3	43	150 (68 Kg.)	5′10″	15	35	1,270	2 days	104.0	200 cc. 50% sucrose; lumbar puncture	75.1
3	Trauma	12	43	220 (99.8 Kg.)	5′ 6″	10	55	1,230	3 hrs.	98.0	None	74.2
4	Normal	8	37	250 (113.4 Kg.)	5′11″	50	6	1,400	3 hrs.	99.6	None	78.1
5	Alcoholic	8	50	140 (63.5 Kg.)	5′ 6″	130	10	1,435	10 hrs.	103.6	200 cc. 25% dextrose	81.6

have retained some water. The method, however, was the same for the control brains as for those from traumatized heads, and all were reduced to constant weight. In subsequent experiments the fat content of the brains was determined. Differences were found, but no correlation could be seen between fat content and water retention. The residue of the normal brain yielded 45 per cent of fat, that of the alco-

23. Skelton, H.: Storage of Water by the Various Tissues of the Body, Arch. Int. Med. **40**:140 (Aug.) 1927. Broemser, in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, p. 64.

24. Nuzum, F., and Le Count, E.: The Ability of Brain Tissue to Take Up Water in Delirium Tremens and Other Conditions, J. A. M. A. **67**:1822 (Dec. 16) 1916.

25. Sauerbruch, F.: Entwicklung und Stand der Hirndrucklehre, Zentralbl. f Chir. **64**:703, 1937.

holic brain 56 per cent and that of the traumatic specimens 58, 49 and 59 per cent. No correlation could be found with the age, weight or height of the patient.

The deficiency in water content was thought to be an agonal or post-mortem phenomenon, yet this would probably apply equally to the normal and to the alcoholic brains. It was thought that the terminal high temperature in cases of head trauma might have induced a pre-agonal water fixation or a postmortem water loss. Two of the patients with injured heads had terminal temperatures of 104 and 104.8 F., but the third, with identical loss of water, had a temperature of 98 F.

The patient with alcoholism, with abundant fluid, also had a terminal temperature of 103.6 F.

The brains from traumatized heads were heavier than normal yet gave up less water and gave up what they did yield with more diffi-culty. One possible explanation is that in trauma to the head there is a shift of parenchymatous fluid from an intercellular to an intracellular position.[26] The water-binding power of the cells, *Wasserverbindungs-vermoege,* increases, and the water cannot be broken off even by the method of chemical dehydration used. Morphologically there is no satisfactory method of demonstrating this intracellular fluid. It is difficult to see where the dry, hard, lumpy material which is left after dehydration could hide extra water. It is possible, however, and other dehydration methods were tried in an effort to blast off more water without changing the general results. While it is admitted that some water may still be hidden unreleasably, a second explanation for the discrepancy between increased weight of the brain and decreased yield of water was offered by Dr. R. Vaughan, in the possibility that the extra weight is accounted for by innumerable petechial hemorrhages scattered into the brain substance.[27] These can be demonstrated micro-scopically (illustration), and added together may account for the increase in weight.[28] At the suggestion of Dr. A. C. Ivy, this was checked by determining the iron content of a second group of brains studied in a similar manner.

26. Jones, I., and Gortner, R.: Free and Bound Water in Cells, J. Phys. Chem. **36**:367, 1932. Gamble, J. L.: Epilepsy: Evidences of Body Fluid Volume Dis-turbance, Arch. Neurol. & Psychiat. **23**:915 (May) 1930.

27. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934. Cassasa, C.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. **24**:101, 1924. Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhage. Arch. Neurol. & Psychiat. **22**:1001 (Nov.) 1929.

28. Schaller, W. F.; Tamaki, K., and Newman, H. W.: The Nature and Significance of Multiple Petechial Hemorrhages Associated with Trauma of the Brain, Arch. Neurol. & Psychiat. **37**:1048 (May) 1937. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, ibid. **32**:257 (Aug.) 1934.

In this group the brains were dehydrated by heat in a constant temperature oven at 80 C. Higher temperatures were not used because of errors which might be induced by volatilization of some of the fats. Even at 80 C., some break-up of fat probably occurred. While the losses from dehydration were somewhat greater in this group than in the first, we feel that this may be partly due to fat loss and that the heat method is not quite as trustworthy as the chemical methods. The results, however, with 1 exception, were relatively similar to those obtained by the previous method. The normal brain yielded 79.5 per cent of water, and the alcoholic brain 82 per cent. Two of the brains from traumatized heads yielded 78.4 and 77.7 per cent of water respec-
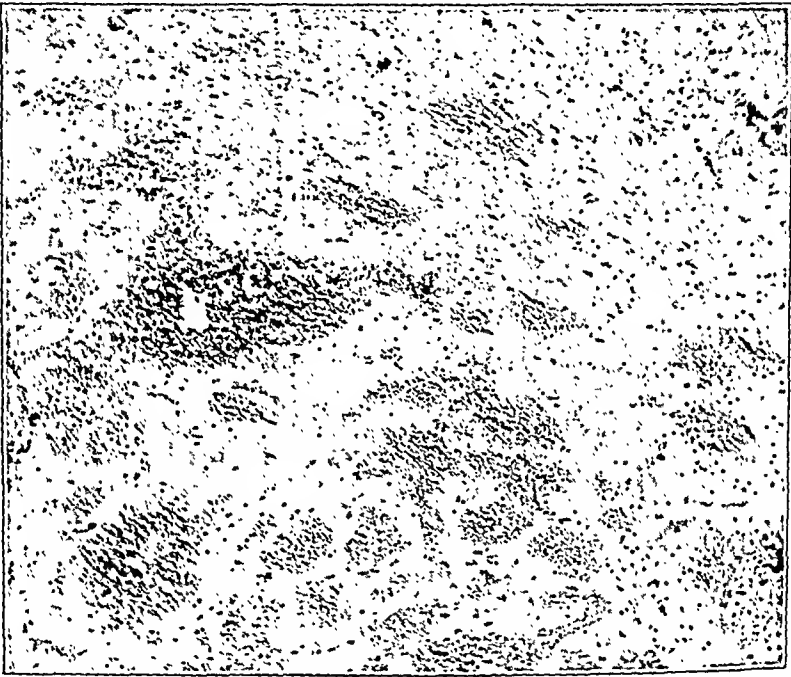
Multiple petechial hemorrhages scattered through the brain substance.

tively. The third specimen was the only one which yielded an abundance of cerebrospinal fluid. In this brain the sulci were widened and the convolutions flattened. There were cerebral lacerations, with a considerable amount of blood mixed in the subarachnoid spaces. This brain yielded 81.2 per cent of water. The patient from whom this specimen had been taken differed from the other patients with trauma to the head in two respects which may account for the difference in result: He had been given 400 cc. of 25 per cent dextrose intravenously; the secondary osmotic shift of dextrose may have been responsible for pouring fluid back into the brain and into the subarachnoid spaces. Further, on looking up his old records at the Cook County Hospital it was found that the patient had been hospitalized for

three bouts of delirium tremens during the last six months before his final admission with an injury to the head. The alcoholism alone might account for the extra fluid. In this group of brains also, 1 of the patients with a "dry" brain had a terminal temperature of 103 F. while the other had a temperature of 100 F. Both patients with alcoholism had high terminal temperatures. The differences in water content of the brain cannot, therefore, be explained by terminal temperatures.

The brain residues in this group were ashed in a muffle furnace at 600 C. Total ash weights could not be determined, because calcium carbonate is added to the material during the ashing process in order to prevent loss of iron. The method of Farrar [29] was used to determine the iron content. With the amount of iron determined, its equivalent in

TABLE 2.—Dehydration of Brain Substance by Heat .

| Case No. | Condition | Hours After Death | Patient | | | Subarachnoid Fluid, Cc., Ventricular Fluid, Cc. | Weight of Brain, Gm. | Terminal Temperature, F. | Survival After Admission | Treatment | Percentage of Water in Brain | Blood in Brain Substances, Cc. per 100 Gm. | Percentage of Fat in Residue |
			Age	Weight, Lb.	Height								
6	Trauma	7	47	170 (77.1 Kg.)	5'10"	8 30	1,450	103.4	20 hr.	200 cc. 50% sucrose; lumbar puncture	78.4	32.5	55
7	Trauma	15	38	165 (74.8 Kg.)	5'8"	10 50	1,535	100.0	6 hr.	None	77.7	37.1	49
8	Normal	6	50	160 (72.6 Kg.)	5'9"	34 6	1,450	99.4	1 hr.	None	79.5	33.4	45
9	Alcoholism	4	46	155 (70.3 Kg.)	5'8"	150 12	1,090	102.0	2 hr.	None	82.0	31.5	56
10	Trauma; alcoholism	4	54	145 (65.8 Kg.)	5'4"	110 25	1,190	107.0	2 days	400 cc. 25% dextrose; lumbar puncture	81.0	33.4	50

blood was calculated. One gram of ox hemoglobin contains 3.4 mg. of iron (the figure for ox hemoglobin is the one usually employed). At a hemoglobin level of 100 per cent there is 15.8 Gm. of hemoglobin per hundred cubic centimeters of blood in males and 13.8 in females. (All the patients in this series were men.) One hundred cubic centimeters of male blood is therefore represented by 53.7 mg. of iron, and the same amount of female blood by 46.9 mg. of iron.

29. Farrar. G.: Determination of Iron in Biologic Materials, J. Biol. Chem. **110**:685, 1935. The ash is dissolved in hydrochloric acid and evaporated to dryness on a steam bath. To the residue, dilute hydrochloric acid is added, with enough water to make up 100 cc. To a 5 cc. portion of this. 2 cc. of hydrochloric acid is added and heated to boiling. One drop of concentrated nitric acid is added to oxidize the iron to the ferric form. Water is added to make up a volume of 25 cc. To this 5 cc. of 20 per cent potassium sulfocyanate and 5 cc. of isoamyl alcohol are added. The reddish color which appears and is extracted by the alcohol is compared with a standard of 0.01 mg. of iron treated in the same way.

By these calculations from determinations of the iron content the normal brain was found to have 33.4 cc. of blood per hundred grams of brain substance, the alcoholic brain 31.5 cc., and the 2 brains from heads with simple trauma 35.2 and 37.1 respectively. This would represent the blood in the vessels plus the blood extravasated in multiple minute hemorrhages. It does not represent gross hemorrhage, as grossly hemorrhagic areas were avoided in taking the samples. With a standard brain weight of 1,400 Gm. these differences would mean that the brains yielding an average of 2.7 cc. of blood more per hundred grams of brain substance would contain 37.8 cc. more of blood altogether. This alone could account for most of the difference in weight between brains from traumatized heads and normal brains.

The alcoholic brain could be estimated to average 26.6 cc. of blood less than the normal brain. The alcoholic brain yielded 33.4 cc. of blood

TABLE 3.—*Dehydration of Brain Substance by Preliminary Acetone Extraction*

Case No.	Conditon	Hours After Death	Patient			Subarachnoid Fluid, Cc.	Ventricular Fluid, Cc.	Weight of Brain, Gm.	Survival After Admission	Terminal Temperature, F.	Percentage of Water		Blood in Brain Substance, Cc. per Gm.	
			Age	Weight, Lb.	Height						Gray Matter	White Matter	Gray Matter	White Matter
11	Normal	6	38	186 (84.4 Kg.)	5'4"	60	8	1,245	3 wk.	102.6	80.47	68.55	36.16	28.1
12	Trauma	10	45	168 (76.2 Kg.)	5'8"	12	45	1,530	2 days	103.0	77.14	65.06	39.09	29.28
13	Trauma	11	40	150 (68 Kg.)	5'6"	6	35	1,420	2 days	102.4	77.89	66.07		

per hundred grams of brain substance, i. e., exactly the same as the normal brain. Whether this is experimental variation or means that the effects of alcohol and trauma neutralized each other is uncertain.

In the light of Pilcher's recent work [8] a third group of brains was studied to determine the effect of head trauma on gray and white matter separately. A third and more rapid method of dehydration was used to meet the possible objection that the slow methods permit oxidation of fat. Gray and white matter were separated. Each sample was extracted with acetone. The residue was placed in a desiccator, and the acetone fraction was dried in an oven at 60 C. The results were relatively the same. In both the normal brains and brains from injured heads, gray matter contained about 12 per cent more water than did white matter. Gray matter also contained more blood. In the brains from injured heads the gray and white matter each contained about 3 per cent less water than did the corresponding parts of the normal brains, and each contained more blood. The gray and the white matter are affected by trauma in

about the same way. Pilcher in his experimental work could find no conclusive evidence of any noticeable post-traumatic cerebral edema. He suggested that intracranial blood volume is of greater importance than cerebral edema in increasing intracranial pressure after trauma.

COMMENT

The findings for absolute water content depend somewhat on the method of dehydration. All heat methods are open to the error introduced by volatilization of fat, and this would tend to increase the figures for water content. Slow oxidation of fat, on the other hand, tends to decrease the value for water yield. For purposes of comparison a uniform method must be used. Within the limits of each method, however, the observations were remarkably constant. It may be that during life these conditions do not obtain, but certainly one can state that after death the brain of a traumatized head is not edematous but dry. Subarachnoid fluid is not increased but decreased. The ventricular component, however, is increased. The brain does not contain less blood than normal, but more.

In the traumatized head the brain is accordingly swollen but not edematous; the swelling is not due to increased water but to increased blood content. How much of the blood in a traumatized brain is inside the vessels and how much is functionless, extravasated blood was not determined in these studies. The brain may have more blood within it yet may suffer functional cerebral anemia. Separation of the two factors is extremely difficult in autopsic specimens. It would have been possible to wash out the intravascular blood first by perfusion. Determinations of iron after perfusion would have given the quantity of extravasated blood alone. The intravascular component could then be determined by estimations of the iron content of the perfusion fluid. Perfusion would have spoiled the determinations of water content and has therefore not yet been done. It will be applied, however, in the experimental approach which is now in progress, so that these two factors will be separated. Even when the analysis is carried to the point of splitting off the extravascular blood component, the question of intravascular functional blood in brain of a traumatized head will not be settled. Quantity of blood is not synonymous with function of blood. Changes in general flow velocity within the brain and especially differential changes in velocity of flow in the various elements of the vascular tree within the brain will have to be determined before the functional factor of blood is understood. In the meantime it might still be possible to establish an increased quantity of specifically intravascular blood in the brain of a traumatized head and still have, for instance through precapillary stasis, a functional cerebral anemia.

While the differences in blood content are significant, the actual figures obtained for blood content as calculated by the iron determination method cannot be accepted at face value because the nonhematic iron of brain substance is included in these determinations along with the hematic intravascular iron. The nonhematic iron of the brain varies with the portion of brain studied and with the age of the patient.[30] The large sample method used in our studies and the fact that our patients were all in the same age group make the differences reliable. We cannot determine the actual hematic iron fraction in our studies by subtracting a known nonhematic iron constant, because although many determinations of the iron content of normal and pathologic brains have been made, the reports do not specify whether the material was first cleared of hematic iron by perfusion.[31] The direct determination of the circulating blood content of the brain by the collargol method [32] is the only feasible approach. This, however, requires experiments in vivo and cannot be done on autopsic material. The difference between this estimate and the total iron content of the brain will give the nonhematic iron constant. How the collargol method will apply to the extravasated blood fraction in the presence of trauma remains to be seen, but the results will probably be irregular.

There was no constant correlation between the autopsic observations and the period of survival after admission to the hospital. In 4 cases of trauma the time of the accident was not known. The known period of survival varied from three hours to two days. Autopsy was done between three hours and eighteen hours from the time of death. No significant difference was attributable to this variation.

The 3 patients with injured heads who lived for more than a few hours had been given 50 per cent sucrose intravenously and one or two lumbar punctures. One patient who lived for two days and 3 who lived for only a few hours were given neither treatment. In this small series we could find no significant differences in the autopsic observations for the two groups. All had about the same dryness of the subarachnoid spaces and brain tissue, about the same ventricular distention and the same somewhat more variable increase of blood content. It may be that at death many differences are canceled. It may be that when the

30. Weil, A.: Vergleichende Studien über den Gehalt verschiedener Nervenbestandteile an Asche, Ztschr. f. physiol. Chem. **89**:349, 1914.

31. Alexander, L., and Myerson, A.: Minerals in Normal and in Pathologic Brain Tissue, Studied by Micro-Incineration and Spectroscopy, Arch. Neurol. & Psychiat. **39**:131 (Jan.) 1938.

32. Weil, A.; Zeiss, F., and Cleveland, D.: The Determination of the Amount of Blood in the Central Nervous System After Injection of Hypertonic Solutions, Am. J. Physiol. **98**:363, 1931.

traumatized brain with or without treatment has been swollen by extravasated blood or by unreleasable intracellular water to a certain end point, the patient dies.

From this material we cannot draw any direct conclusions as to the relative efficacy of various therapeutic procedures. Some conclusions as to pathogenesis, however, may be drawn, and by these conclusions certain lines of therapeutic effort are at least suggested. The patient with an injured head is suffering primarily from uncontrolled internal hemorrhage within the cranial cavity. As the multiple extravasations of blood, together with some intracellular binding of water and the ventricular dilatation, begin to swell the brain, there is a spontaneous effort on the part of the brain tissue, even without treatment, to compensate by decreasing the fluid in the subarachnoid spaces and by decreasing the quantity of intercellular fluid within the brain substance. Lumbar puncture could assist in the first process and intravenous sucrose in the second. When the damage has been too great, both the spontaneous and applied therapeutic mechanisms fail, and the patient dies.

Dehydration is the proper treatment, but perhaps some agent is needed which will more effectively than sucrose split intracellular fluid from within the brain cells. Yet one must recognize that the water binding may be in part a salutary, physiologic defense reaction of the injured cells and that it should not be disturbed too vigorously. It may be that the limits of usefulness of chemical methods of dehydration have been reached.

The dilatation of the lateral ventricles by the brain swelling shutting off the foramens is significant. Relief of the internal traumatic hydrocephalus by ventricular puncture and drainage may be a useful approach in correcting cerebral compression.

Procedures to decrease parenchymatous hemorrhage are of unquestioned value. These include: (1) absolute rest; (2) avoidance of abrupt reduction of intracranial pressure by lumbar puncture within the first six hours, because it is just this pressure which diminishes hemorrhage; (3) limitation of intravenoclysis at first to small quantities, 300 to 400 cc., because raising the blood pressure might cause recurrence of hemorrhage; and (4) for patients in extreme shock. small blood transfusions.

CONCLUSIONS

1. In autopsic material. the subarachnoid fluid in cases of trauma to the head is not increased but decreased.

2. The ventricular fluid is increased in the presence of internal traumatic hydrocephalus.

3. The brain in an injured head at death is not wet but dry; it is swollen but not edematous.

4. Part of the enlargement of the brain in cases of head trauma is a result of ventricular distention.

5. Part of the swelling of the brain after trauma to the head is accounted for by increased blood content from innumerable petechial hemorrhages. (This increment was computed from determinations of iron in the brain specimens. The method did not separate intravascular from extravascular blood. The findings are relative, because the non-hematic iron fraction was not separated from the hematic iron. Further analysis by the experimental method is outlined.)

6. For the remainder of the swelling of the brain in cases of trauma to the head the factor of unreleasable intracellular parenchymatous fluid can be assumed only by exclusion.

7. The lines of therapeutic effort suggested by this study indicate that lumbar puncture and dehydration are indicated but have probably been carried as far as possible. Ventricular drainage may be useful. Emphasis is placed on measures to reduce parenchymatous hemorrhage within the brain substance.

EXPERIMENTAL PRODUCTION OF TUMORS OF THE BRAIN WITH THE SHOPE RABBIT PAPILLOMA

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Cutaneous papillomas developing in rabbits inoculated with the virus of infectious papillomatosis [1] possess the characters of mammalian tumors [2] and are readily susceptible to autotransplantation. Bits of hashed papilloma tissue implanted in muscle, subcutaneous tissue and inner organs of the host proliferate actively, invading or displacing adjacent tissue. In the absence of bacterial infection, cellular reaction about the growing implants is notably scanty; frequently none is present. Under these conditions the growth is a slowly enlarging mass which has little apparent effect on the surrounding tissues other than that attributable to pressure or to physical interference. This character of the transplanted papilloma has suggested its use in the study of the effects of pressure inside the cranial cavity. With this in mind, the behavior of the papilloma on implantation in various sites within the skulls of domestic rabbits has been studied. The results obtained are described in the present paper.

1. Shope, R. E., and Hurst, E. W.: Infectious Papillomatosis of Rabbits, with a Note on Histopathology, J. Exper. Med. **58**:607-624 (Nov.) 1933. Beard, J. W., and Wyckoff, R. W. G.: The Isolation of a Homogeneous Heavy Protein from Virus-Induced Rabbit Papillomas, Science **85**:201-202 (Feb. 19) 1937.

2. Rous, P., and Beard, J. W.: A Virus-Induced Mammalian Growth with the Characters of a Tumor (the Shope Rabbitt Papilloma): I. The Growth on Implantation Within Favorable Hosts, J. Exper. Med. **60**:701-722 (Dec.) 1934. Beard, J. W., and Rous, P.: II. Experimental Alterations of the Growth of the Skin; Morphological Considerations; the Phenomena of Retrogression, ibid. **60**: 723-740 (Dec.) 1934. Rous, P., and Beard, J. W.: III. Further Characters of the Growth; General Discussion, ibid. **60**:741-766 (Dec.) 1934; The Progression to Carcinoma of Virus-Induced Rabbit Papillomas (Shope), ibid. **62**:523-548 (Oct.) 1935.

<center>METHOD</center>

The virus employed in the production of papillomas for transplantation was obtained from warts occurring spontaneously in cottontail rabbits. Warts which had been stored in 50 per cent glycerin solution for several months were rinsed in distilled water, ground in the usual way with sand and extracted in a 5 per cent suspension with 0.9 per cent sodium chloride solution. Cleared of gross particles by low speed centrifugation, the suspension was filtered by suction through a Berkefeld N candle. An abdominal area about 3 cm. in diameter was shaved, lightly scarified with sandpaper and inoculated by rubbing into it a few drops of the virus suspension.

The histologic structure of the cutaneous papilloma has been described in detail.[3] In brief, the virus causes rapid proliferation of the epidermal cells of the innermost or basal layer, giving rise to protruding papillae. With broadcast inoculation of the virus, as in the present instance, the papillae coalesce, and the growth appears eight to twelve days after inoculation as a confluent layer of papilloma tissue.

When the layer had reached a height of 1 or 2 mm. the fine hair in and about the growth was removed with dilute barium sulfide. The area was gently scrubbed with soap, thoroughly rinsed in running tap water, dried with sterile sponges and then wet with 70 per cent alcohol. With a razor which had been kept in 70 per cent alcohol for thirty minutes the superficial layer of the growth was sliced off; this was discarded. The deeper layer was then shaved away in a thin slice, placed in 1 cc. of sterile 0.9 per cent sodium chloride solution and thoroughly hashed with knives.

Through a midline incision in the scalp, an opening 1.5 mm. in diameter was made in the skull in the desired region. Implantation directly into the brain was accomplished by injection of a few of the fragments of papilloma through a short 18 gage needle ground smooth at the end. When extradural implantation was intended, the dura was gently separated intact from the skull, and a few fragments of papilloma tissue were pushed with a probe through the opening in the skull. For subdural implantation the dura was punctured without separation from the skull, and fragments were pushed gently through the opening with a probe. In the last instance, dural incision was confirmed by the appearance of subarachnoid fluid. The defect in the bone was closed with wax containing a fragment of lead for roentgenographic localization, and the incision in the scalp was closed with silk. Strict precautions for the maintenance of asepsis were observed throughout.

The rabbits were allowed to live for varying periods subsequent to transplantation; they were killed by means of illuminating gas.

<center>GENERAL CHARACTER OF GROWTHS RESULTING FROM
INTRACRANIAL TRANSPLANTATION</center>

The papilloma proved readily transplantable to the subdural space. Growths produced in this region in rabbits DR 97 and DR 598, killed forty-one and forty-two days respectively after subdural implantation, are shown in figures 1 and 2. The growths in both instances were

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3. Footnotes 1 and 2.

situated directly beneath the original osseous defects, and their location in relation to the cortex corresponded to the rostral portion of Brodmann's area 17 as demarcated for the rabbit brain.[4] The masses were firmly embedded in the cortex, could not be dislodged by gentle manipulation and were covered by dura except in the region of the original incision, where the membrane appeared adherent to them. In shape they were flattened spheres; they were elastic and well encapsulated, and the presenting surface of each was irregular and creamy white. On section the external layer and its inward extensions showed as a
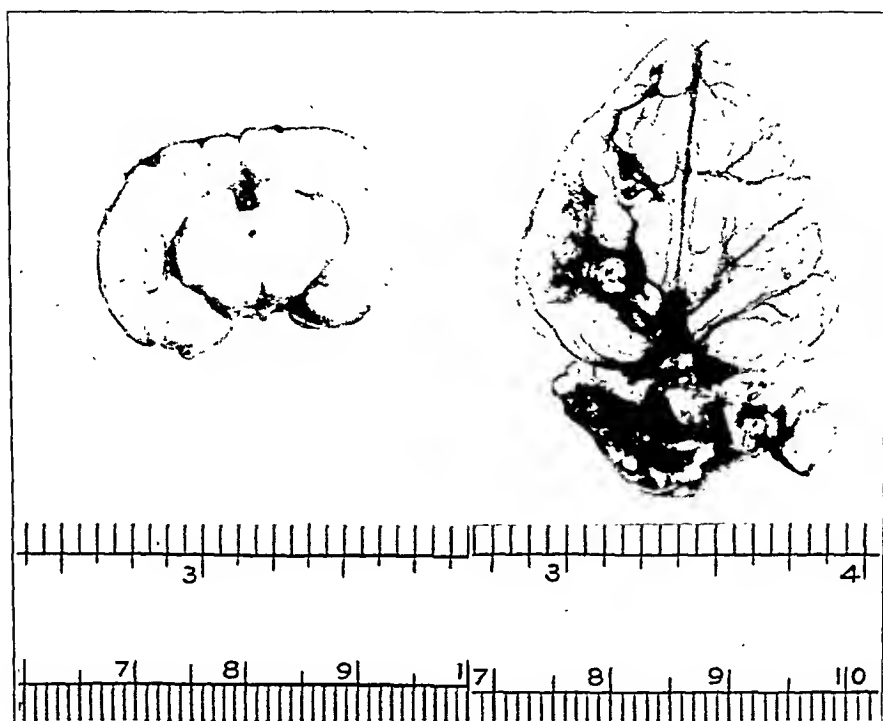
Fig. 1.—Subdural tumor. × 2.

rind of whitish living tissue about a dense, concentrically striated creamy or grayish black necrotic mass. No connective tissue capsule was evident on macroscopic examination. Although the masses were adherent to the underlying cerebral tissue, transition from developing nodule to cortex was very abrupt. The papillomatous pattern was recorded externally by blunt irregularities of the proliferating basal epithelium.

4. Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues, Leipzig, Johann Ambrosius Barth, 1909, vol. 12, figs. 106 and 107.

This was represented in the interior by sharper papillae that penetrated the necrotic center. The proliferative activity of the external layer appeared unimpaired, but there was a distinct inability on the part of the epithelial columns to invade the surrounding tissue. There was no change in the portion of the skull adjacent to the tumors.

The subdural tumor from rabbit DR 97 measured 7.2 by 6 by 10 mm. Its outer surface protruded 3 mm. above the surrounding cortical tissue, and its inner surface impinged on the ventricular wall, causing a decided
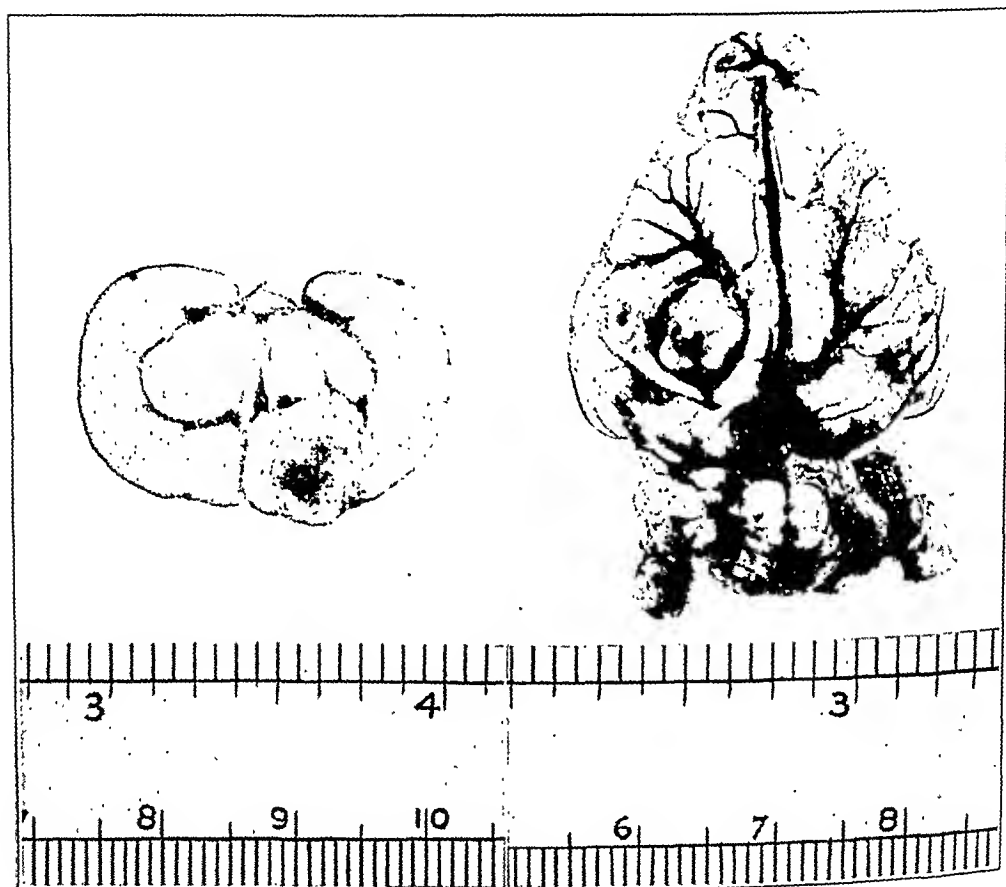
Fig. 2.—Subdural tumor, × 2.

distortion of the ventricular system. The tumor nodule produced in rabbit DR 598 measured 6 mm. in diameter and 4 mm. in cross section. It protruded 2 mm. above the surrounding cortical tissue and involved only the gray matter of the cortex in its growth. The proliferating epithelial layer in the smaller tumor was more regular than that in the larger nodule. The disparity in size or rate of growth of the masses in the 2 animals during the same period may be attributed to the development of the tumor from a single focus in the latter rabbit rather than from the coalescence of multiple foci, which probably occurred in the former.

Extradural implantation of the papilloma likewise resulted in the production of typical, actively proliferating transplants in 2 animals, rabbits DR 98 and DR 99, killed forty-two days and twenty-one days, respectively, after extradural implantation. One such growth is shown in figure 3. The growths, situated over the rostral part of area 17 of the cortex, in both instances were attached to the skull and were covered by a continuous dural sheet adherent to their surfaces. The dural surface of each mass was smooth, exhibiting only faint irregularities suggestive of the papillomatous character of the growth. No gross

Fig. 3.—Extradural tumor, × 2.

reaction was evident in the dura. The growths were not attached to the cortex, and when they were removed a smooth, oval indentation was left in the brain tissue. On section, these extradural nodules were similar to those produced by subdural implantation.

The extradural implantation in rabbit DR 98 was made over the left hemisphere by pushing the hashed papilloma tissue into place with a probe. When the brain case was removed, a column of proliferating epithelium was observed to have penetrated the osseous defect externally and to have produced a small growth, measuring 4 mm. in diameter,

outside the skull. The extradural mass was 7.5 by 8.5 by 6 mm., and the indentation in the cortex was 4 mm. in depth. In rabbit DR 99, implantation outside the dura was made on the right side; on the left

Fig. 4.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver-lithium carbonate stain; × 230.

side, however, fragments of papilloma were injected directly into the brain tissue through an 18 gage needle. No tumor developed on this side. The extradural growth over the right cerebral cortex was approxi-

mately 4 mm. in diameter. It was dislodged during the removal of the bone case, and more accurate measurements were not obtained. The indentation in the cortex was correspondingly shallow, being scarcely 2 mm. in depth.
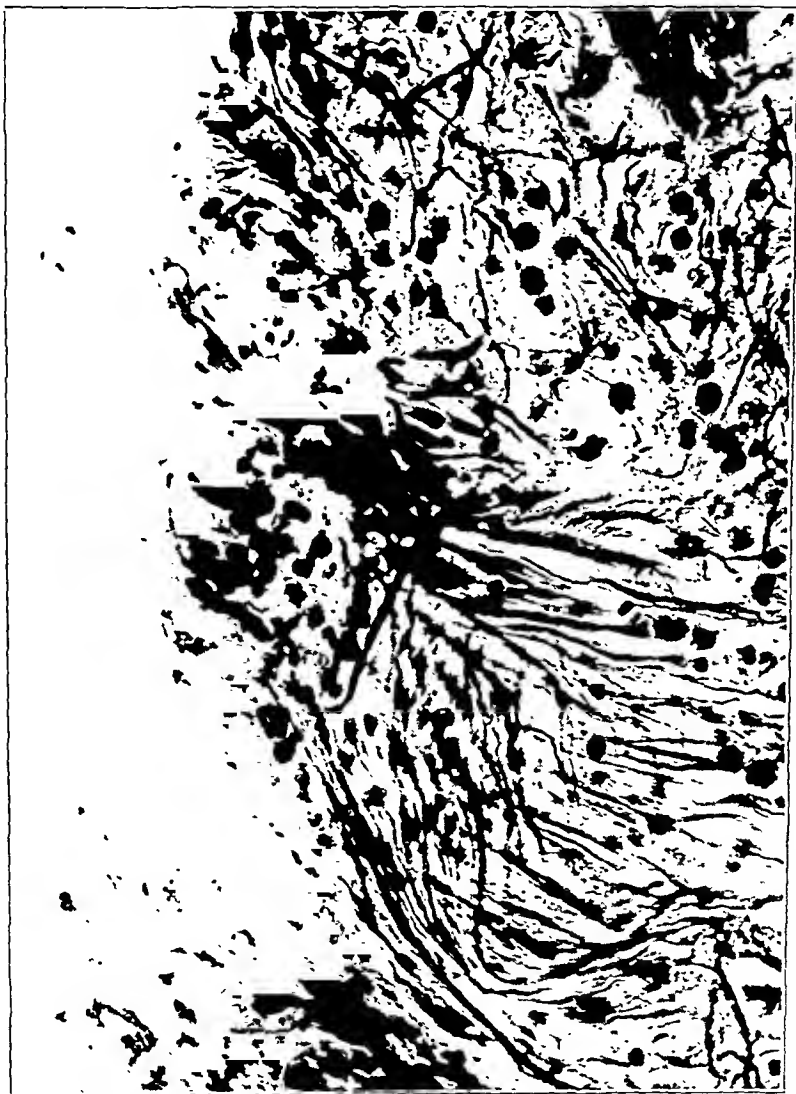
Fig. 5.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver-lithium carbonate stain; × 485.

Attempts were made to implant the papilloma intracerebrally in 2 other rabbits (DR 415 and DR 402) by injecting fragments of papilloma directly into the brain tissue through an 18 gage needle. Sixteen days

and eighteen days after implantation, respectively, the animals were killed.
No intracerebral tumors were found. In rabbit DR 415 a tiny extra-
dural nodule was found at the site of injection.
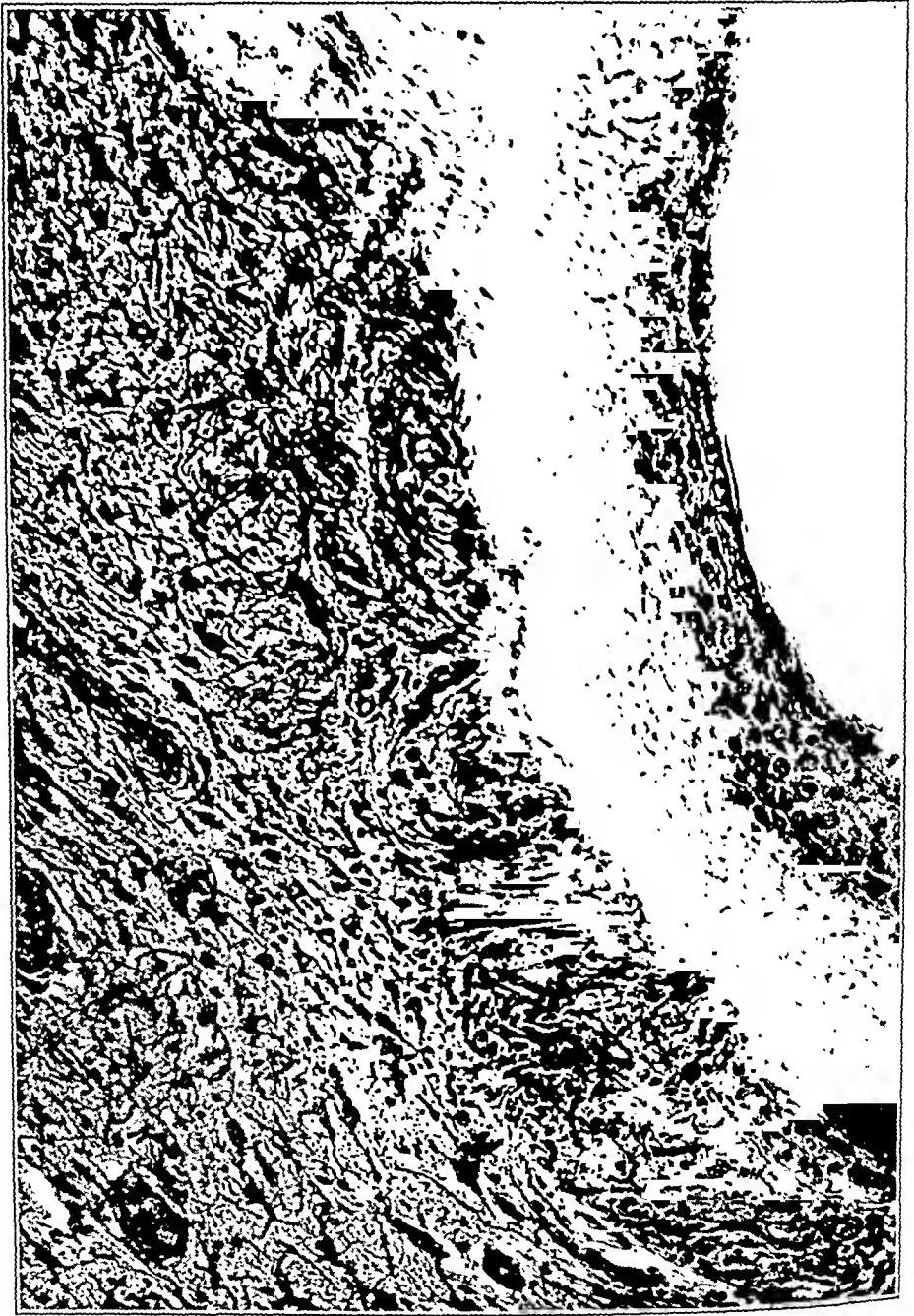
Fig. 6.—Astrocytic reaction to subdural tumor in rabbit DR 98. Silver-
lithium carbonate stain; × 375.

REACTION OF CEREBRAL TISSUE TO THE IMPLANTED PAPILLOMA

Specimens were cut through the center of the transplants or through
the cerebral defects caused by the extradural masses, and the tissues

were fixed in Cajal's formaldehyde–ammonium bromide solution. Blocks were taken and frozen sections cut to include growths and adjacent brain tissue. These were stained, after the appropriate time of fixation, with
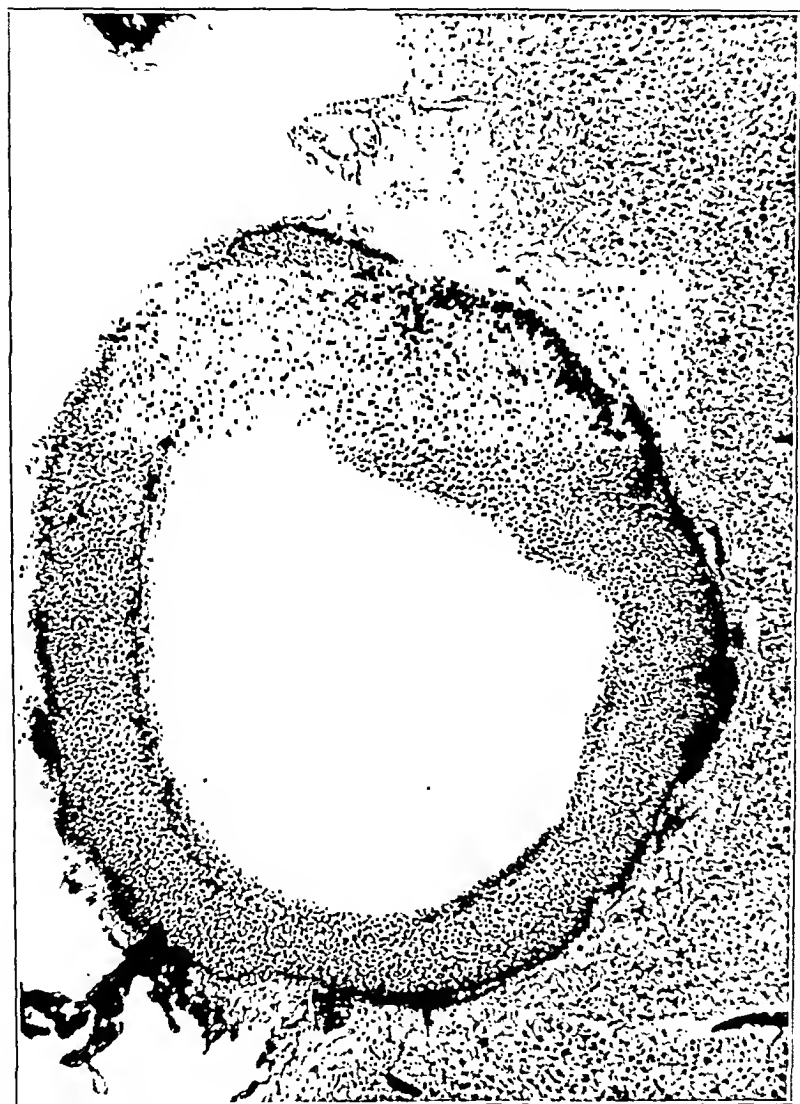
Fig. 7.—Subdural tumor of rabbit DR 598, showing early glial reaction. Silver–sodium carbonate stain; × 145.

(1) Penfield's second modification of Rio-Hortega's silver sodium carbonate stain [5]; (2) Rio-Hortega's silver–lithium carbonate stain, and

5. Penfield, W.: A Method of Staining Oligodendroglia and Microglia (Combined Method), Am. J. Path. 4:153-157 (March) 1928.

(3) Cajal's gold chloride sublimate method. Other blocks were taken for staining with hematoxylin and eosin.

A part of the subdural growth of rabbit DR 97 was separated from the brain by a thin membrane of pia mater. In some areas this was
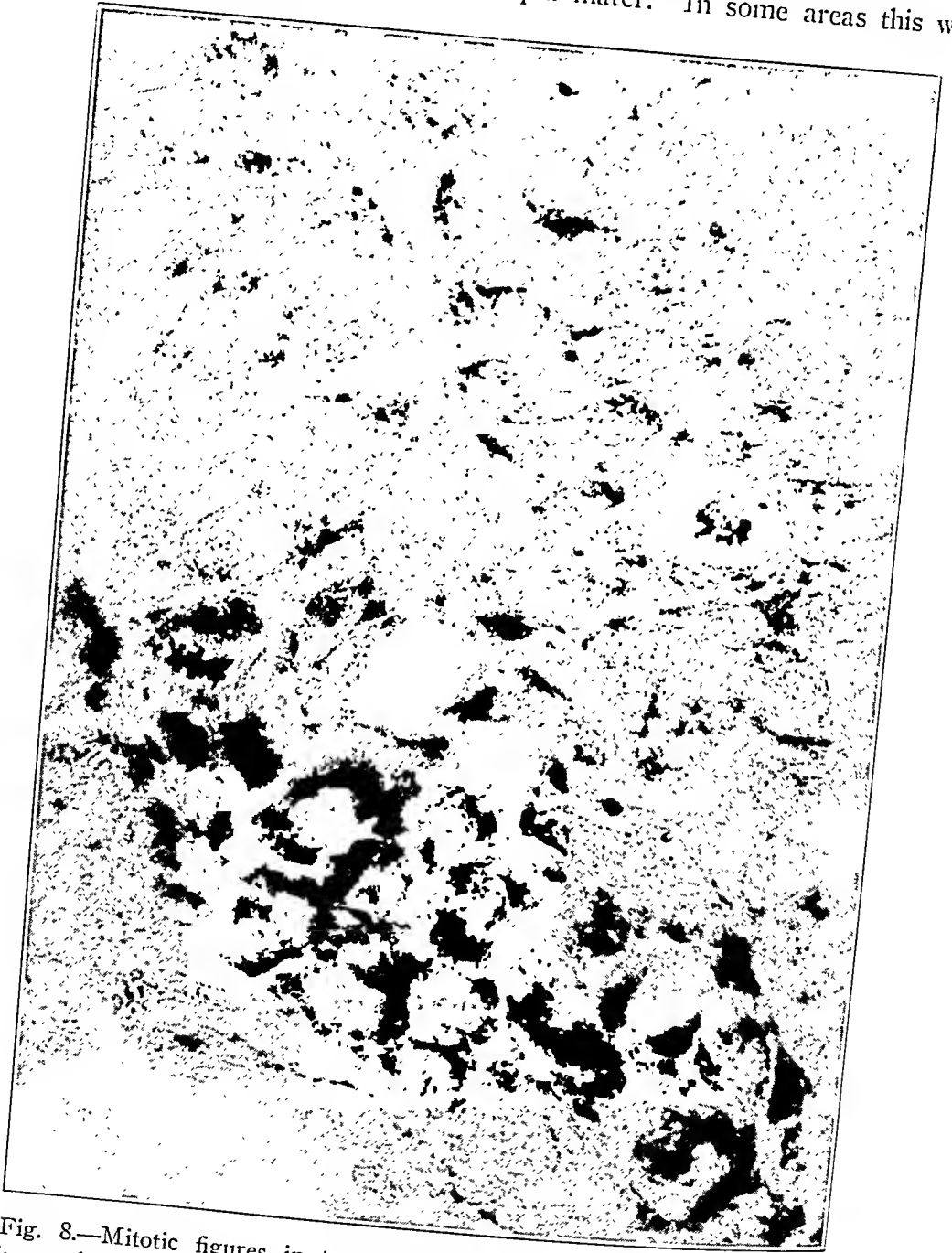
Fig. 8.—Mitotic figures in transplanted tumor of rabbit DR 598. Silver-sodium carbonate stain; × 485.

absent, and the tumor cells were in direct contact with the depressed cortex. The glial reaction was very different in these two regions. Where the pia was present there was no noticeable change in either the

microglia or the astrocytes beneath it; even the microglia lying adjacent to the pial membrane appeared normal. In areas where there was no membrane between the tumor and the brain, marked and extensive glial reaction was present. There was proliferation of fibrous astrocytes with

Fig. 9.—Compression of brain by extradural tumor of rabbit DR 98. Silver–sodium carbonate stain; × 65.

formation of a dense mass of glial fibers (figs. 4, 5 and 6). These fibers were attached to the tumor, and many individual fibers could be seen surrounding one or more of the tumor cells. Only in rare instances did the fibers penetrate into the tumor. This sharp demarcation between

Fig. 10.—Increased cellularity with normal glia beneath extradural tumor in rabbit DR 98. Silver–sodium carbonate stain: × 230.

the astrocytic fibers and the tumor was clearly demonstrated in the specimens stained with gold chloride sublimate; in these the processes were stained deeply, and the tumor was very pale. The cortical neurons were obviously destroyed in the areas of dense gliosis. Many astrocytes with abnormally large cell bodies were lying next to the tumor.

There was uniformly a striking increase in the number of small blood vessels in the outer margin (away from the tumor) of this gliosis. A number of these vessels showed intimal and adventitial thickening suggestive of that commonly seen in association with glioblastoma multiforme in man. In one area there was thrombosis of several medium-sized vessels. Here the astrocytes were larger and their processes were fragmented (clasmatodendrosis). Also, in this area the microglia showed all changes, from thickening of the processes of the cells near the edge of the area to typical compound granular corpuscles (*Gitterzellen*) in the center. This region presented the usual picture of cerebral necrosis. Elsewhere the microglia appeared unchanged.

The tumor of rabbit DR 598 was much smaller than that of rabbit DR 97. Changes similar to those described for the latter were present, but to a lesser extent. The dense glial reaction was just beginning to form (fig. 7). In both tumors many mitotic figures were present in the tumor cells (fig. 8). The papillomas remained discrete, however, and the neoplastic cells did not invade the brain.

The extradural tumor of rabbit DR 98 had greatly compressed the adjacent gray matter, as may be seen in figure 9. The compressed area stained less deeply with the silver sodium carbonate stain. No cellular changes were seen in the neuroglia or microglia. The photomicrograph (fig. 10) was taken at the square marked on figure 9 and shows normal microglia lying next to the tumor. There was, however, increased cellularity in the cortex beneath the tumor, apparently caused by compression only. The cell bodies of the cortical neurons were apparently unchanged by the compression; however, we cannot be certain of this with the stains used for this tissue. The apical dendrites of the neurons were shortened, often curved and occasionally tortuous ("corkscrew processes"). No increased vascularity was seen; the fact that the microglia cells were normal would indicate that the flow of blood through this area had been diminished little if at all for any appreciable length of time.

SUMMARY

Experimental intracranial tumors have been produced in rabbits by extradural and subdural implantation of the cutaneous papilloma induced by the virus of infectious papillomatosis. The intracranial growths were similar in gross characteristics to those observed following transplantation of the papilloma in other organs and in other tissues of the rabbit.

In contrast to the behavior of the growth on implantation in other tissues, with the possible exception of the kidney and the stomach,[2] there was noted an inability of the proliferating epithelium to invade adjacent tissue. When even a thin layer of meninges lay between the tumors and the brain, there was a minimum of glial reaction present. On the other hand, whenever the tumor came in direct contact with the brain, there was astrocytic proliferation with the formation of numerous fibers, many of which were attached to the tumor. Where such gliosis was heaviest there was increased vascularity, and thrombosis occasionally occurred, producing localized areas of necrosis with microglial reaction.

The growth characters of this transplanted cerebral tumor suggest its use in the study of various problems involving intracranial pressure as they may be applied to the central nervous system of the rabbit. Indeed, the tumor appears to offer suitable material for the study of tissue response to slowly developing pressure in any region in which successful implantation can be accomplished. Immediate problems related to the central nervous system are the production of papillomatous tumors within the substance of the brain and a further and more detailed study of the reaction of the brain to the transplants and to prolonged pressure.

THE SUPERIOR COLLICULI

THEIR FUNCTION AS ESTIMATED FROM A CASE OF TUMOR

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The function of the collicular bodies of the quadrigeminal plate in man, and particularly that of the superior (or anterior) colliculi, remains undetermined. Not only has little experimental work been devoted to the problem, but little suitable human material has been available for study. The case which will be reported here seems ideal in many respects, and we feel that its presentation is worth while.

COMPARATIVE ANATOMY AND PHYSIOLOGY OF THE COLLICULI

Studies in evolution show that the function and importance of the tectum mesencephali have been steadily regressive.[1] In the very early vertebrates, such as the bony fishes, the tectum consists of a relatively large bilobular body situated on the alar plates that cover the aqueduct. These corpora bigemina (in selaceans) are exclusively visual in function. The expanded portion of the alar plates serves as the end station of the somesthetic pathway.

Beginning with the amphibians and progressing through reptiles and birds, two more colliculi make their appearance, i. e., the inferior, colliculi, which subserve a function of audition. Even in birds, however, the superior colliculi are the association centers of vision and assume such importance in this respect as to be termed the lobus opticus.

The importance of the tectum mesencephali in these vertebrates can be understood when one realizes that it is the associational mechanism for visual, auditory and somesthetic reflexes. It is not surprising to find that its cellular structure is complex. Cajal resolved the lobus opticus in birds into three series of strata: an external formation of seven layers of nerve cells and fibers, an intermediate formation of five layers and an internal formation of two layers. The first stratum is a layer of optic fibers derived from the optic tract.

1. Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, ed. 2, New York, Paul B. Hoeber, 1923, pp. 485-525 and 782.

As the mammal is approached, however, this great complexity and importance are lost to such an extent that the corpora quadrigemina appear almost vestigial. Thalamization (which begins in birds) and telencephalization rob the tectum of its visual, auditory and somesthetic importance.

One can hardly doubt, however, that these bodies continue to function in man in certain reflex capacities.

AFFERENT AND EFFERENT CONNECTIONS OF THE COLLICULI

The superior colliculi present an outer stratum zonale and three gray strata. The cortex is the homologue of the cortex of the optic lobe in birds.

Afferent Connections of the Superior Colliculi (fig. 1).—1. Fibers running from the retina through the optic tract (these constitute a small
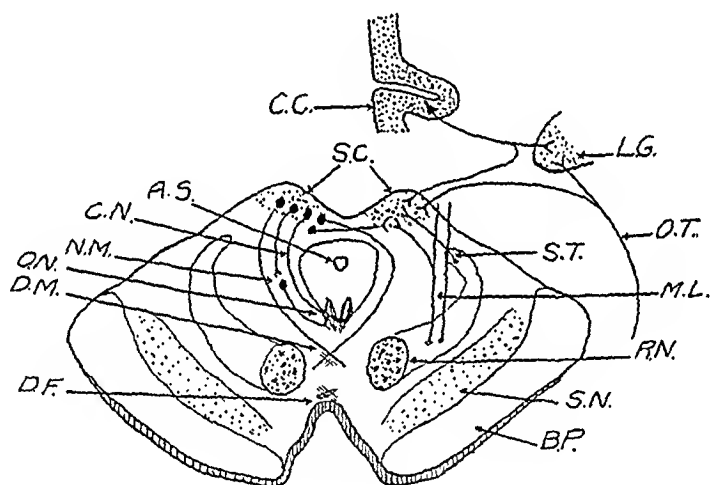
Fig. 1.—Diagrammatic representation of the better known connections to and from the superior colliculi. Afferent connections are shown on the right and efferent connections on the left. *C.C.,* calcarine cortex; *S.C.,* superior colliculi; *L.G.,* lateral geniculate body; *O.T.,* optic tract; *S.T.,* spinotectal tract; *M.L.,* medial lemniscus; *R.N.,* red nucleus; *S.N.,* substantia nigra; *B.P.,* basis pedunculi; *D.F.,* decussation of Forel; *D.M.,* dorsal tegmental decussation of Meynert (fountain decussation of Meynert). This tract proceeds as the praedorsal bundle and tectospinal tract. *O.N.,* oculomotor nuclei; *N.M.,* nucleus of the medial longitudinal fasiculus; *C.N.,* colliculonuclear tract to the nuclei of the extraocular muscles; *A.S.,* aqueduct of Sylvius.

proportion of optic fibers, and none of them subserve the function of vision).

2. Fibers from cells about the calcarine fissure.

3. Fibers from the spinotectal tract.

4. Collaterals from the medial lemniscus (probably proprioceptives from muscles and tendons).

Efferent Connections of the Superior Colliculi.—1. Fibers from the superior colliculus to the nuclei of the oculomotor mechanism (the colliculonuclear tract). Arising from large cells in the fourth layer, one portion decussates (fountain decussation of Meynert) and one portion continues direct. The fibers end in the nuclei of the oculomotor, trochlear and abducens nerves.

2. The tectospinal tract, which passes by way of the internal arciform fibers to the dorsal tegmental decussation of Meynert. It descends, in relation with the posterior longitudinal fasciculus, into the ventral white column of the spinal cord.

The following paragraph is taken from Rasmussen:[2]

The better known connections of the superior colliculus (primary visual reflex center) consist of fibers from the optic tract, from the visual cortex and from the spinal cord (spino-tectal fasciculus). Collaterals from other tracts passing up and down also enter the superior colliculus. From the nucleus of the superior colliculus fibers go to the various centers, including the nucleus of the posterior commissure and the nucleus of the medial longitudinal fasciculus, (centers connected with ocular movements, with the vestibular system and with the corpus striatum), the oculomotor and trochlear nuclei, the pons (by means of fasciculus tectoponticus), and the spinal cord (by means of fasciculus tectospinalis). The nucleus of the medial longitudinal fasciculus, in turn, discharges downward into lower centers. The center for upward gaze and associated movement of the eyelids and raising of the brow is generally considered to be in the neighborhood of the superior colliculus, most likely in the dorsal part of the reticular formation just lateral to the upper end of the oculomotor nucleus.

Afferent Connections of the Inferior Colliculi.—Fibers from the lateral lemniscus of the homolateral and of the contralateral side.

Efferent Connections of the Inferior Colliculi.—Fibers running by way of the inferior brachium to the tegmentum of the cerebral peduncle and thence to the thalamus and cortex of the temporal lobe.

Both pairs of colliculi have commissural connections.

FUNCTION OF THE SUPERIOR COLLICULI

The superior colliculi have been thought to play a role in two important functions: (1) the pupillary light reflex and (2) the associated or conjugate movements of the eyes. Controversy has arisen concerning each of these functions.

For purposes of analysis and comparison, we have given some attention to observations recorded in cases of tumor of the pineal gland and of tumor of the third ventricle.

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2. Rasmussen, A. T.: The Principal Nervous Pathways, New York, The Macmillan Company, 1932.

REVIEW OF REPORTED CASES OF TUMOR OF THE QUADRIGEMINAL PLATE

Most of the tumors of the quadrigeminal plate which have been reported were discarded because they were obviously too extensive to be of analytic value. In table 1 a list of cases is given in which the lesion appears to have been reasonably limited to the tectum. There was practically no impairment of the pupillary light reflex. What mention was made of associated movements implied that they were impaired or lost.

Wilson and Gerstle[3] reported 2 cases which might serve for more detailed elaboration. These authors were more interested, however, in defending the claim that tumor can cause Argyll Robertson pupil.

TABLE 1.—*Tumor of the Quadrigeminal Plate*

	Pupillary Reaction		Associated Movements	Tumor	Comment	Author
	Light Reflex	Accommodation				
1.	Good	?	Poor	Confined to Q. plate posterior to aqueduct	....	Bristowe[8]
2.	Good	?	?	Tubercle of Q. plate extending to pons	3d nerves paretic	Kolisch[8]
3.	Good	Good	Bilateral ophthalmoplegia	Tubercle of Q. plate	....	Sachs[8]
4.	Good	Good	?	Tubercle, size of hazelnut posterior to aqueduct	....	Goldzieher[8]
5.	Good	?	?	Gliosarcoma of Q. plate	Pupils unequal; patient partly blind	Taylor[8]
6.	Very sluggish	Very sluggish	?	Large glioma of Q. plate	Pupils irregular and dilated; nystagmus	Glaser*
7.	Good	Good	?	Walnut-sized glioma of Q. plate	Internal strabismus	Glaser*

* Glaser, M. A.: Brain **52** : 226-262, 1929.

Their first patient exhibited widely dilated pupils which did not react to light directly or consensually. Reaction to accommodation was prompt. Ocular movements were limited and poorly sustained both to right and to left, although upward and downward associated movements appeared normal. There was slight internal strabismus of the right eye, with ptosis of the right lid and nystagmus on deviation to the right. At postmortem examination, however, it was seen that the tumor, in addition to having destroyed the anterior colliculi, filled the fourth ventricle and invaded the pons.

3. Wilson, S. A. K., and Gerstle, M.: Argyll Robertson Signs in Mesencephalic Tumors, Arch. Neurol. & Psychiat. **22**:9-18 (July) 1921.

Their second patient also showed absence of the pupillary light reflex without impairment of the accommodation reflex. Conjugate upward deviation of the eyes showed pronounced limitation. Conjugate lateral movements were of good range except for some defect in lateral movement of the left eye. Associated downward movements were fair. At autopsy, however, there was revealed a large cystic tumor which, in addition to flattening the left anterior colliculus, extended into the anterior portion of the thalamus and reached from the upper limit of the pons to the corpus callosum.

In a like manner, Wilson and Rudolf [4] reported a case of Argyll Robertson pupil. Conjugate lateral movement of the eyes was well performed to the right but poorly performed to the left. Upward associated movement was poor and downward associated movement impossible. Autopsy revealed a tumor invading the splenium of the corpus callosum and starting to grow into the third ventricle. The ventricular aspect of both thalami and the hypothalamus were invaded. The authors stated that, most significant of all, the tumor had invaded and destroyed the anterior colliculi and that the signs pointed unmistakably to invasion of this region.

Tumor of the Pineal Body.—Among the signs attributed to this tumor are ptosis, loss of upward associated movements of the eyes and macrogenitosomia praecox in young boys. The first two of these signs have been thought to be due to pressure on the superior colliculi.

A study of these cases (tables 2 and 3) shows that Argyll Robertson pupils are occasionally but by no means commonly found. Ptosis is rare. Impairment of some form of associated ocular movements is not uncommon and is most commonly paralysis of upward associated movements.

Tumor of the Third Ventricle.—In reference to the third ventricle, the following is quoted from a complete paper by Fulton and Bailey.[5]

Pupillary disturbances are frequently seen. Argyll Robertson pupils have been reported (Ford, 1924) but are more commonly associated with pineal and midbrain tumors. In cases of tumor of the third ventricle, they are probably due to involvement of the mid-brain.

Paralysis of conjugate eye movements was noted by Weisenburg (1911) but are more characteristic of tumors of the mid-brain and pineal body (Horrax, 1927).

Pupillary Light Reflex.—That the Argyll Robertson pupil can be caused by pathologic conditions other than syphilis is well established,

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4. Wilson, S. A. K., and Rudolf, G.: Case of Mesencephalic Tumor with Double Argyll Robertson Pupil, J. Neurol. & Psychopath. **3**:140-143, 1922.

5. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:261-277, 1927.

but syphilis (of the tabetic or dementia paralytica type) is by far the commonest cause.

Merritt and Moore [6] reviewed the works of Karplus and Kreidl, Lenz, Ranson and Beattie and concluded that the fibers which subserve

TABLE 2.—*Tumor of the Pineal Gland*

	Pupillary Reaction		Associated Movements	Tumor	Comment	Author
	Light Reflex	Accommodation				
1.	Good	?	Poor	Tumor 3.5 × 2 × 1.5 cm.	Bilateral paralysis of 6th nerve	Glaser *
2.	Good	?	?	Tumor 2.5 cm. in diameter	Embedded in the Q. plate	Dandy †
3.	Good	Good	Unable to elevate eyes	Parapineal tumor 2.8 cm. in diameter	Paralysis of the right 6th nerve	McLean ‡
4.	Poor	Good	?	Tumor size of walnut	....	Harris §
5.	Absent	Good	Good	Tumor 2.5 cm. in diameter	Bilateral paralysis of external rectus	Globus and Silbert #
6.	Sluggish	?	Limitation of upward gaze	Tumor 2 × 2 × 3 cm.	Paralysis of right external rectus	Globus and Silbert #
7.	Absent	Good	Paralysis of upward gaze	Large tumor	Ptosis of right eyelid; weakness of right external rectus	Globus and Silbert #
8.	Sluggish	?	?	Tumor 7 × 6 × 8 cm.	Ptosis of right lid; paresis of external recti	Globus and Silbert #
9.	Sluggish	Good	?	Tumor, 5 cm. in diameter	Bilateral weakness of internal rectus	Globus and Silbert #
10.	Sluggish	?	Lost to right	Large cystic tumor	Ptosis of right lid; patient became deaf	Globus and Silbert #

* Glaser, M. A.: Brain **52** : 226-262, 1929.
† Dandy, W. E.: Arch. Surg. **33** : 19-46, 1926.
‡ McLean, A. J.: Surg., Gynec. & Obst. **61** : 523-533, 1935.
§ Harris, W., and Cairns, H.: Lancet **1** : 3-8, 1932.
# Globus, J. H., and Silbert, S.: Arch. Neurol. & Psychiat. **25** : 937-985, 1931.

TABLE 3.—*Summary of Ocular Signs Associated with Tumors of the Pineal Gland* *

Blindness or impairment of vision	45	Conjugate deviation	3
Diplopia	16	Paralysis of fourth cranial nerve	3
Paralysis of upward movement	15	Paralysis of all extraocular muscles	3
Paralysis of sixth cranial nerve	15	Paralysis of downward movement	3
Immobility of one or both pupils	14	Unilateral ptosis	3
Nystagmus	12	Bilateral ptosis	1
Internal strabismus	5	External strabismus	1
Paralysis of third cranial nerve	4	Constriction of pupil	1
Argyll Robertson pupils	3	Rhythmic convergence spasm	

* Taken from a paper by K. O. Haldeman (Tumors of the Pineal Gland, Arch. Neurol. & Psychiat. **18** : 724-744 [Nov.] 1927). The paper is a complete report of 113 cases of tumor of the pineal gland, taken from the literature to 1927.

6. Merritt, H. H., and Moore, M.: The Argyll Robertson Pupil: An Anatomic-Physiologic Explanation of the Phenomenon, with a Survey of Its Occurrence in Neurosyphilis, Arch. Neurol. & Psychiat. **30** :357-373 (Aug.) 1933.

the light reflex pass from the optic tract with the brachium of the superior colliculus to the cephalad end of the superior colliculus. A portion of the fibers cross in the dorsal portion of the posterior commissure while the remainder arch ventrally toward the oculomotor nuclei.

Paralysis of Associated Ocular Movements.—The influence of the cortex on ocular deviation deserves brief consideration here. Conjugate deviation as a result of irritative and destructive lesions of the cortex is demonstrated, to be sure, in epileptic seizures and sudden destructive lesions. The effects are transient because of bilateral representation of voluntary ocular movement. The existence of cortical "eye turning centers" in the frontal, temporal and occipital lobes has been definitely established. Those in the temporal and occipital lobes are probably associated with cortical auditory and visual functions, respectively. The cerebral cortex, however, has to do with the voluntary direction of visual gaze and not with reflex conjugation or associated movement of the paired visual organ. The function of maintaining the eyes in a conjugate relation is clearly relegated to structures in the mesencephalon. The problem of present concern is whether the superior colliculus subserves or is indispensable to this function.

That the maintenance of conjugate focus is not and cannot be controlled by voluntary effort alone would seem to be clearly demonstrated by a simple experiment: If the visual fields are separated by a partition between the eyes, any existing muscular imbalance quickly renders the eyes aphoric. No amount of voluntary effort can correct the hyperphoria or maintain correction of the esophoria or exophoria.

As one studies motor function, a plan always stands out in clear relief. The cerebral cortex is responsible for the voluntary initiation and direction of movements, but when the muscles are contracted, and while they are being contracted, various phenomena of synergy and coordination are controlled by reflex arcs which begin in the muscle that is being contracted. In the instance of associated ocular movements, the afferent arc begins in the retina.

Spiller [7] stated that the evidence is strong that paralysis of associated lateral movements of the eyeballs is indicative of a lesion of the posterior longitudinal bundle. He also stated that it is true that lateral associated movements have been impaired, with paralysis of upward or downward associated movements, in a number of instances as they were in some of his cases, but a lesion in the vicinity of the corpora quadrigemina will better explain this form of paralysis than will a lesion of the cerebral cortex. He continued that because certain of his

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7. Spiller, W. G.: The Importance of Clinical Diagnosis of Paralysis of Associated Movements of the Eye-Balls, Especially of Upward and Downward Associated Movements, J. Nerv. & Ment. Dis. **32**:417-497, 1905.

patients who had lesions in the tegmentum, not involving the corpora quadrigemina, exhibited various forms of associated paralysis a coordinating center in the colliculus is improbable. For example, in a case in which there was paresis of upward associated movement the lesion was posterior to the oculomotor nucleus and did not involve the quadrigeminal plate.

Many cases are cited by Posey and Spiller [8] which presented various combinations of paralysis of association, and in all instances parts in the region of the aqueduct of Sylvius were implicated.

The following summary is quoted from Spiller : [7]

As a result of my studies, I believe that persisting paralysis of associated lateral movement indicates a lesion of the posterior longitudinal bundle; that persisting paralysis of upward or downward movement indicates a lesion in the vicinity of the oculomotor nucleus, and that paralysis of associated ocular movements is not the result of a lesion of extracerebral nerve fibers. Lesions of the cerebral cortex may certainly cause paralysis of lateral associated ocular movements, and possibly of upward and downward associated ocular movements, but cortical paralysis of associated ocular movements is transitory, unless possibly where the center on each side of the brain is destroyed. Paralysis of associated ocular movements may be caused by hysteria. Any case in which associated ocular palsy is persistent, and is of organic nature, is unsuitable for operation unless the operation is merely palliative, as the lesion is probably within the posterior part of the pons or cerebral peduncle, according to the form of the associated palsy, or else causes much pressure upon the dorsal portions of these structures. The paralysis of associated ocular muscles may be produced by inflammatory lesions or lesions of a similar character (alcohol, syphilis) as well as by tumor, and may disappear later in the course of the disease. Syphilitic ependymitis or cellular infiltration must be considered in diagnosing the lesion causing paralysis of associated ocular movements. Most congenital associated palsies are probably nuclear in origin.

Spiller stated that all the pathologic evidence he had been able to obtain in cases of persistent palsy of upward or downward movement is indicative of a lesion near the aqueduct of Sylvius, and that it is extremely doubtful whether a lesion confined to the corpora quadrigemina and causing no pressure on the surrounding parts ever causes paralysis of associated ocular movements. Those who favor such a view have not produced proof of a supranuclear center in this part.

He quoted Topolanski as saying that electrical irritation of the corpora quadrigemina of the rabbit does not produce ocular movements and that these parts can be removed without producing symptoms.

Bernheimer, cited by Spiller, has shown by experiments on monkeys that normal ocular movements do not depend on the integrity of the

8. Posey, W. C., and Spiller, W. G.: The Eye and Nervous System: Their Diagnostic Relations, Philadelphia, J. B. Lippincott Company, 1906.

corpora quadrigemina, thus refuting Prus's statements that a center for ocular movements does exist in this structure.

Spiller has collected cases in which the corpora quadrigemina have been destroyed without disturbance in the movements of the eyeballs (Weinland; Seidel; Ruel; Nissen, cited by Von Kornilow).

As the converse of the aforementioned phenomena, Oppenheim [9] observed pseudobulbar paralysis in which lateral movements of the eyeballs were impaired in voluntary innervation but were preserved when the patient tried to follow an object or to turn in the direction from which a sound came.

Wilson and Pike [10] while studying nystagmus found that injury to the corpora quadrigemina did not affect nystagmus but did bring about disjunctive coordination of ocular movements.

Other Symptoms and Signs Associated with Tumor of the Quadrigeminal Plate.—Ataxia: In a case reported by Taylor [11] the cerebellum was normal, but the corpora quadrigemina were flattened, gray and gelatinous (gliosarcoma). The symptoms were ptosis, staggering gait, drowsiness, ataxia of the upper limbs, nearly complete double opthalmoplegia and lateral nystagmus.

Bielschowsky, quoted by Posey and Spiller,[8] pointed out that in the presence of tumor of the corpora quadrigemina the incoordination associated with occasional temporal pallor of the disks may cause one to confuse the condition with multiple sclerosis.

Bruns, cited by Posey and Spiller, emphasized the difficulty in differentiating between tumor of the corpora quadrigemina and tumor of the cerebellum, as ataxia and ophthalmoplegia may be caused by a tumor in either location.

Bruns held that if the symptoms begin with ataxia the tumor is probably in the cerebellum, but Nothnagel contended that if ataxia begins before ophthalmoplegia the diagnosis of tumor of the corpora quadrigemina is favored.

In 2 cases of tumor observed by Turner,[12] staggering gait with diplopia and headache were the chief symptoms. In 1 case there was retropulsion.

Drowsiness and yawning, nystagmus and impairment of vision: These are not uncommon signs of tumor of the corpora quadrigemina but are not pathognomonic and are undoubtedly due to the hydro-

9. Oppenheim, H.: Zur Symtomatologie der Pseudobulbärparalyse, Neurol. Centralbl. **14**:40-41, 1894.

10. Wilson, J. G., and Pike, F. H.: The Mechanism of Labyrinthine Nystagmus and Its Modifications by Lesions in the Cerebellum and Cerebrum, Arch. Int. Med. **15**:31-39 (Jan.) 1915.

11. Taylor, F.: Disease of the Corpora Quadrigemina, Lancet **2**:1252, 1893.

12. Turner, W. A.: Localization of Intracranial Tumors, Brain **21**:341, 1898.

cephalus and increased intracranial tension that result from obstruction of the aqueduct.

FUNCTION OF THE INFERIOR COLLICULI

Although the interest of this paper is chiefly centered on the superior colliculi, it may be stated that audition is the only function which has been related to the inferior colliculi from both anatomic and clinical standpoints. There is considerable controversy as to whether the inferior colliculi are indispensable to auditory perception. Cases that would give evidence for both the negative and the positive answer to the question have been reviewed by Posey and Spiller.[s]

REPORT OF CASE

C. H., a white girl aged 9, was referred to the University Hospital in March 1936 by Dr. L. W. Chain of Dedham, Iowa.

The chief complaints were inability to walk, periods of unresponsiveness, divergent squint, headaches and vomiting.

The child had been delivered by the aid of instruments but otherwise delivery was uneventful.

At the age of 1 year she began to walk, but her parents said that she was always unusually "wobbly'" on her feet. This was especially noticeable when she became old enough to run. She would drag the right lower extremity, with noticeable elevation of the right hip. There was also a tendency to hold the head tilted to the right. Often, on attempting to run, she would stumble for no apparent reason and fall flat with little attempt to catch herself. She was therefore obliged to stand alone at school, being unable to run and play with other children. This motor instability had progressed rapidly during the past few months, and three weeks prior to her admission to the hospital it was necessary to put her to bed because of her complete inability to stand or walk. If seated in a chair, she remained listless and appeared not to be able to use her muscles.

About one year prior to admission she had had a peculiar attack. While going home from school she fell and lay flat. Although she seemed conscious, she would not respond to the other children. After a few moments she arose and proceeded home with no apparent ill effects. She had had about twelve of these attacks. Her mother stated that in some of them she stiffened, with the arms held down and the head back. She had never had a "shaking convulsion." In several of the recent seizures she had stopped speaking in the middle of a sentence, and while she blankly stared ahead, her limbs had fallen limp. If a question was repeated three or four times during the seizure, she would answer.

When the child was 1 year old her mother noticed a developing squint. A futile attempt was made to correct this by glasses.

Although the child slept well, without ever crying out at night, she had complained of headaches for three years, which were relieved by projectile vomiting. She had never complained of dizziness.

She had appeared more drowsy and sleepy during the past six months, and it was necessary to take her out of school the past year, chiefly because of unresponsiveness. She was in the second grade but always found it difficult to learn and particularly to write.

Recently the vision had become poor. Glasses were of no avail.

For the past six months she had occasionally soiled herself as a result of incontinence.

Family History.—The father and mother were both alive and well. Nine siblings were alive and well; none were dead.

Past History.—In addition to the disturbances brought out in the history of the present illness, she had had a "high fever" at the age of 1½ years, at which time she could "hardly breathe." She had begun to walk at one year and to talk at the usual age. She had talked normally in her earlier years.

The past history was otherwise unessential.

Examination.—The child sat perfectly still in a chair with the extremities laxly remaining in any resting position in which one placed them. She was listless, with no apparent interest in her surroundings and with never the slightest play of emotion on her face. If asked a question repeatedly, she might finally give a brief, somewhat explosive answer in a strikingly harsh bass voice. The answer was sometimes unintelligible.

The largest circumference of the head was 58 cm. The eyes showed a divergent squint of 40 degrees. She fixed at times with one eye and at times with the other. Extraocular movements were complete in all four directions but with obviously disjunctive coordination. There was no ptosis, and nystagmus was not elicited. The pupils were equal and regular in outline, reacted well to light individually and consensually and reacted on an attempt to accommodate. There was bilateral choking of the optic disks (2 to 3 diopters), which the ophthalmologist felt was of recent onset and without hemorrhage. Vision was 6/60 in each eye, and the visual fields appeared full to vis-a-vis examination.

Function of the cranial nerves was unimpaired. (Special vestibular tests were not made.) The sensorium seemed normal throughout to tests for pain, light touch, two point discrimination and sense of position, although one of us (O. H.) felt that there was evidence of astereognosis with respect to the right hand.

Although there was evident laxness of the muscles, with hypotonia of all extremities, the strength was good and the grips were 100 per cent.

Reflexes	Right	Left	
Biceps	++	++	
Knee	+++	+++	(pendular)
Achilles tendon	++++	++++	
Abdominal	0	0	
Plantar	Extensor	Extensor	

The Hoffman sign was present on the right and absent on the left. Ankle clonus was sustained on both sides. Alternate movements were badly performed on both sides and with the tongue. She missed badly in the finger to nose test. When she was placed on her feet and asked to walk, there was marked astasia-abasia, with retropulsion and lateropulsion to the right.

General examination of the systems gave essentially negative results. The temperature was normal; the pulse rate, 80, and the blood pressure, 100 systolic and 75 diastolic. The Wassermann reaction was negative.

Although the findings were strongly suggestive of a cerebellar tumor, the history, disjunctive ocular coordination and bass voice suggested the possibility of a more proximal tumor, particularly a tumor of the pineal body or possibly of the third ventricle. Consequently, a ventriculogram was made. Three hundred and eighty cubic centimeters of ventricular fluid was replaced with air, and the ventriculogram revealed symmetric hydrocephalus and a third ventricle dilated to a degree in keeping with the dilatation of the lateral ventricles. The lateral view

did not demonstrate the outline of the third ventricle sufficiently to rule out a pineal tumor, but the findings were accepted as sufficient to warrant a diagnosis of subtentorial tumor.[13]

Judging from the postmortem examination of the brain, the third ventricle should have exhibited its entire contour but with complete obstruction of the
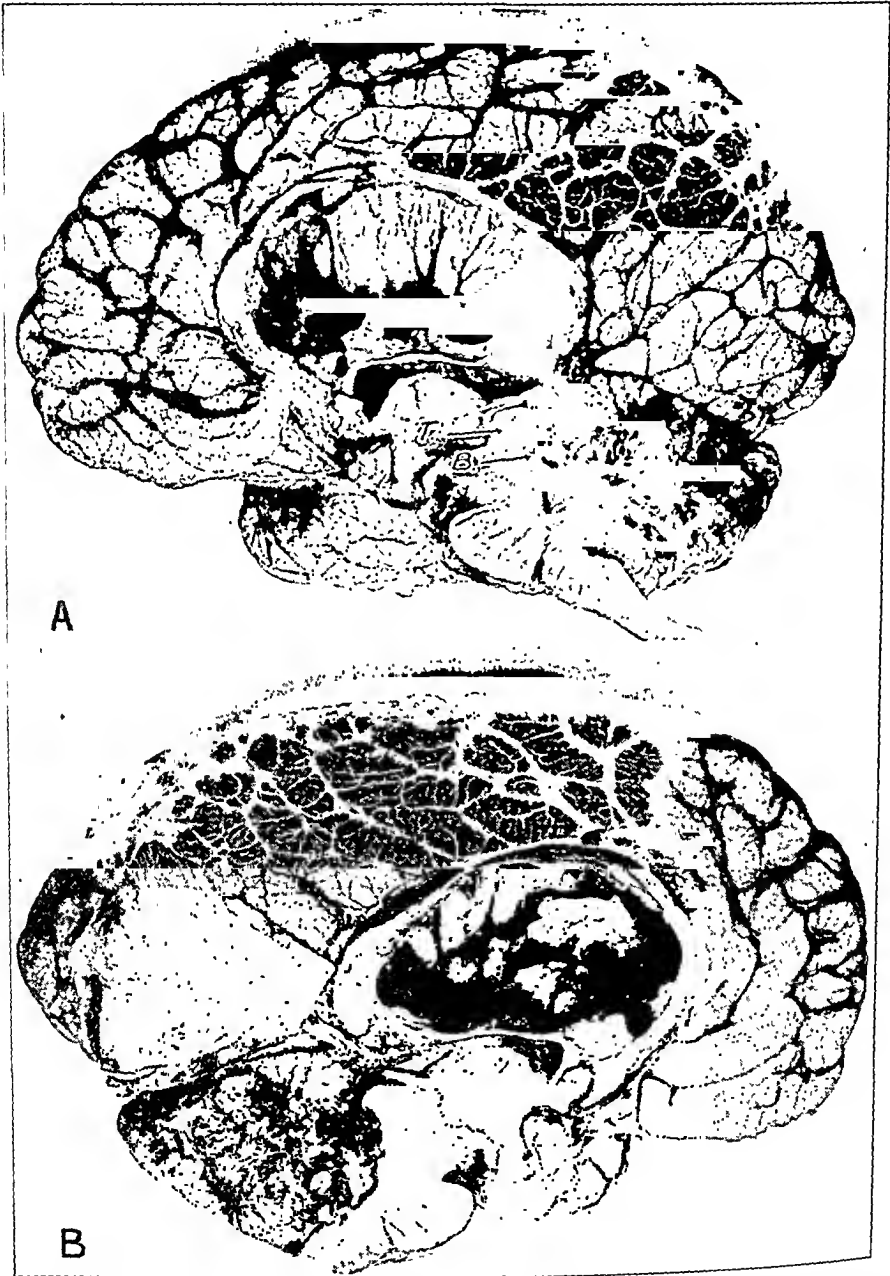
Fig. 2.—The two halves of the brain. *A*, right half; *B*, left half. *T*, tumor, the confines of which are clearly visible; *B*, region of the inferior colliculi from which the biopsy specimen was taken.

13. One of us (O. H.) would no longer accept such an insufficient demarcation of the third ventricle as final but would make further effort to obtain a filling.

aqueduct. This assurance, however, of the absence of a pineal tumor would have had great significance at the time of exploration.

The cerebellum was explored in the usual manner and was found to be devoid of tumor. When air and fluid were released from the ventricles the cerebellum was relaxed, with no tendency to bulge. The vermis was incised in the midline, and a fourth ventricle of normal size was disclosed. An occasional drop of
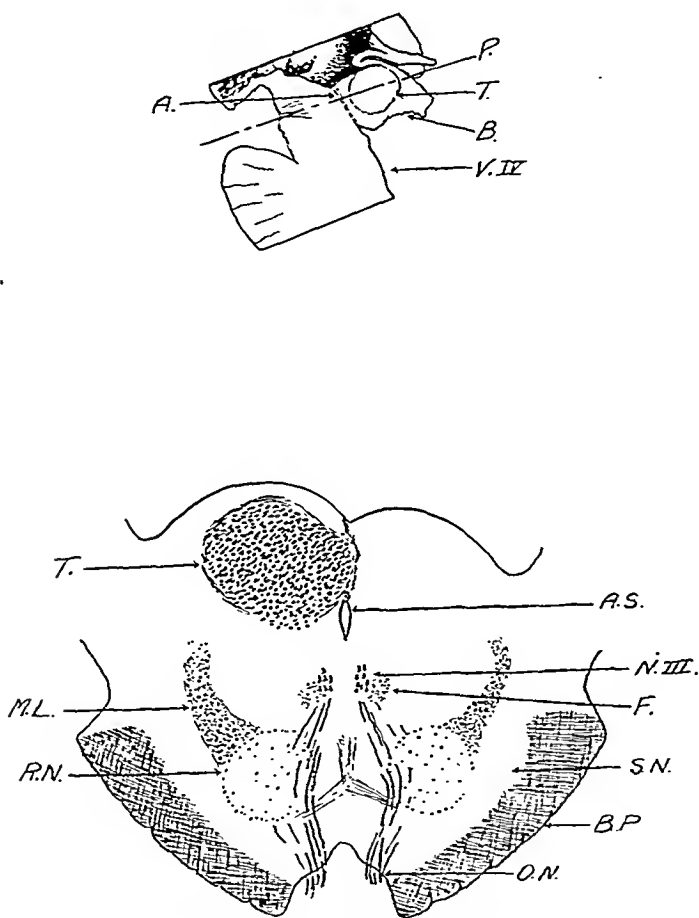
Fig. 3.—Diagrammatic sketches of the mesencephalon. The upper drawing shows only one half of the mesencephalon (mesial view). *A*, aqueduct of Sylvius; *T*, tumor; *B*, region of the inferior colliculi from which a specimen for biopsy was taken; *V*, *IV*, region of the fourth ventricle; *P*, plane of transverse section from which the diagrammatic sketch below was made. Both halves of the mesencephalon were used in the preparation of the lower sketch, which illustrates the tumor in its greatest diameter and also its relation to the more important structures of the mesencephalon. The cells in the nuclei of the ocular nerves showed no pathologic changes. This was true also of the red nucleus. The fibers in the region of the median longitudinal fasciculus were intact. *T*, tumor; *M.L.*, medial lemniscus; *R.N.*, red nucleus; *A.S.*, aqueduct of Sylvius; *N III*, oculomotor nucleus; *F*, medial longitudinal fasciculus; *S.N.*, substantia nigra; *B.P.*, basis pedunculi; *O.N.*, oculomotor nerve.

cerebrospinal fluid issued from the aqueduct. Realizing that the obstruction was at a high point in the aqueduct, the operator was anxious to determine the possibility of a pineal tumor in view of a subsequent operation through the proper exposure. Had the ventriculogram been sufficient to rule out a pineal tumor, there would have been no anxiety or excuse for proceeding further. When the
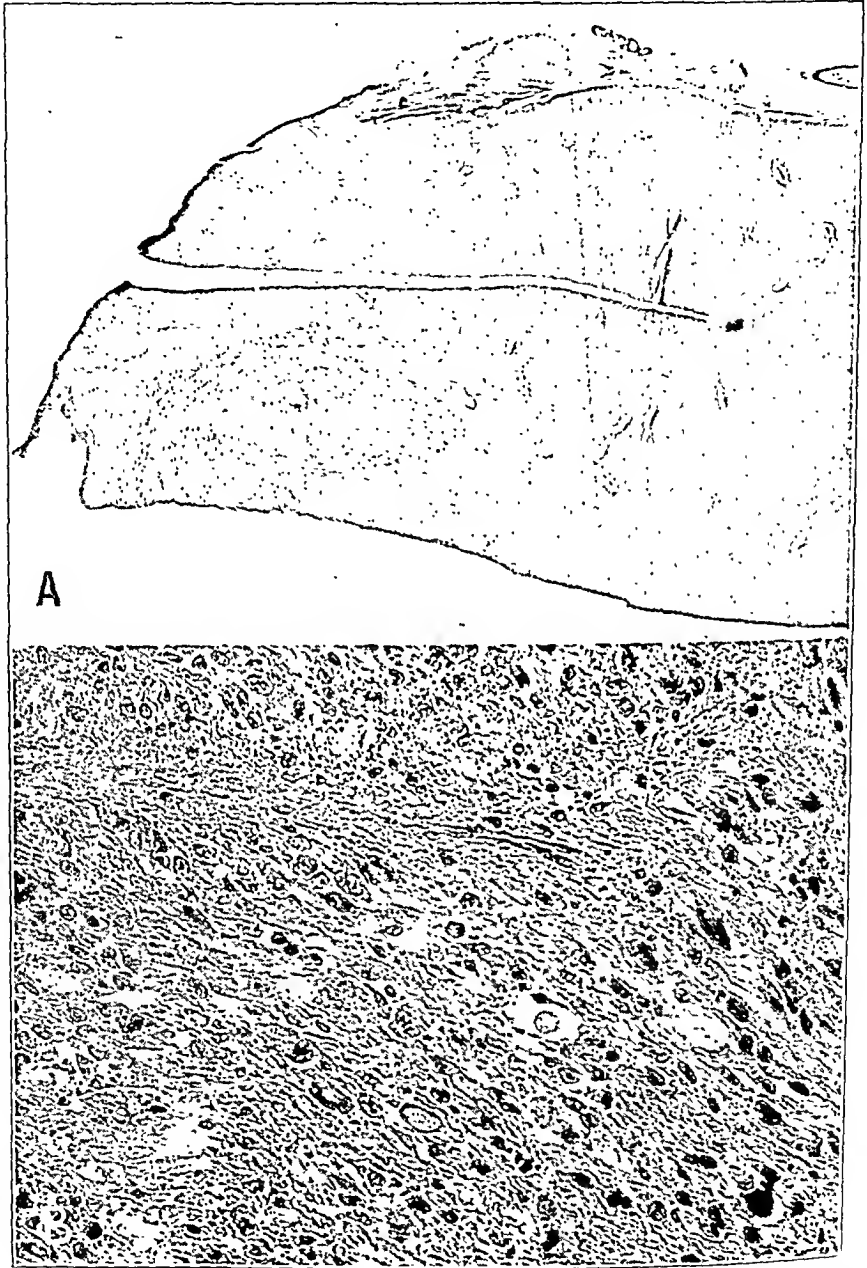
Fig. 4.—*A,* low power photomicrograph of a transverse section of the left half of the mesencephalon (phosphotungstic acid-hematoxylin stain), showing the pseudocapsule and the confines of the tumor. *B,* high power photomicrograph of the section shown in *A,* demonstrating the cellular structure of the tumor.

quadrigeminal plate was reached, a firm globular mass was encountered. Material for biopsy was taken from this in view of the possibility of pinealoma. This later proved to be normal tissue and had been taken from the inferior colliculus.

Shortly after the operation hyperthermia developed, the temperature being 106 F. per rectum, and the extremities were icy cold. There was marked extensor rigidity, with the arms extended and pronated and fists clenched. Cold sponges reduced the hyperthermia, but despite the usual care the patient succumbed fourteen hours after the operation.

Necropsy.—At necropsy a small spherical tumor was observed practically within the confines of the left superior colliculus (fig. 2).

Aside from dilation of the ventricles, nothing unusual was found in the brain. The aqueduct of Sylvius was not completely obstructed. It was patent to a strand of silkworm gut but to nothing larger.

The material for biopsy which had been taken at the time of operation had not included tumor but had been taken from normal inferior colliculus.

Microscopic Studies.—Transverse serial sections were made of both halves of the mesencephalon from just cephalad to just caudad to the tumor. The sections were made 20 microns thick, and every ninth and tenth section was stained with Held's stain and hematoxylin-eosin stain.

Studies of these sections revealed that none of the major nuclei or tracts of the mesencephalon were destroyed except those related to the left superior colliculus (fig. 3).

The pathologic description of the tumor, as given by Dr. Gregory Barer and Dr. William J. Dulin, was as follows (fig. 4): "Situated in the left superior colliculus is a circumscribed oval tumor, measuring between 4 and 5 mm. in its largest diameter. Except for the anterior aspect, the tumor is surrounded by compressed brain tissue, which forms a distinct false capsule. The median posterior raphe is displaced definitely to the right, but the tumor does not invade the right colliculus. Anteriorly the tumor cells can be seen invading normal brain tissue a very short distance.

"The tumor is composed chiefly of large spindle-shaped cells, which tend to have a distinct palisade arrangement. Between these cells is an interlacing mass of fibrils, an occasional large cell suggestive of an astrocyte, and typical tumor giant cells. A rare mitotic figure is present in the spindle-shaped cells. A moderate number of well formed medium-sized blood vessels are observed. No areas of extravasated blood, blood pigment or degeneration are noted.

"The cytologic structure and arrangement resemble more closely the glioblastoma than any other classified type of glioma."

<center>COMMENT</center>

From the foregoing information several facts seem to stand in relief:

1. Although a tumor which extends anterior to the quadrigeminal plate may or may not be associated with a loss of pupillary reflex to light, a tumor which appears to be limited to the superior colliculi or to the quadrigeminal plate is invariably unassociated with this sign.

2. A lesion of the superior colliculi appears to be always accompanied by one or more forms of paralysis of associated ocular movements.

To be sure, lesions variously placed about the aqueduct and anterior to the quadrigeminal plate may cause paralysis of associated move-

ments in various and limited forms. This might be expected and does not dispose of the possibility that the superior colliculus is the "head ganglion" for associated ocular movements.

Our patient had distinct loss of associated movements in all directions, and she fixed with either eye. These disjunctive movements were first noticed at the age of 1 year. In consideration of the remainder of the history, it is reasonable to suppose that the tumor was present at that time and was of such a nature that all signs could be attributed to involvement of the superior colliculus.

The pupillary light reflex was never lost, but from a study of the specimen it could well be that the most cephalad fibers of the colliculus escaped destruction.

While we are reserved about attributing the early ataxia and incoordinate motor phenomena to involvement of the superior colliculi, these signs have been reported in the literature often and consistently enough to deserve some attention, and it is difficult to account for them in this case by any other cause.

In view of the accepted facts concerning the life history of the glioblastoma, it is difficult to correlate the histopathologic character of this tumor with its apparent clinical course.

SUMMARY

A 9 year old girl proved to have a tumor limited to the left superior colliculus of the quadrigeminal plate.

There is clinical evidence that the tumor was present at the age of 1 year.

The pupillary light reflex was present, but there was paralysis of associated ocular movements in all directions. Visual fixation alternated between the eyes.

These, as well as other interesting symptoms and signs, are discussed and correlated with some of the literature concerning the possible function of the superior colliculi.

HEMANGIOMA OF JOINTS

REPORT OF FIVE CASES

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Our purpose is (1) to present 5 cases of hemangioma of the knee joint in which the condition has been diagnosed and treated by us, (2) to set forth the criteria for an accurate diagnosis and the most favorable methods of treatment and (3) to analyze the cases reported in the literature. The peculiar nature of this tumor, the frequency of admitted error in diagnosis and the relative lack of success in its treatment make the 5 cases intensely interesting.

The following series of 5 cases of hemangioma of the knee is the largest reported from any one clinic. To our knowledge radium and roentgen therapy have not been used before in the treatment of this condition. In 2 cases the patients were treated by the accepted methods prior to the use of roentgen therapy. In 3 cases treatment with roentgen rays and radium as suggested by one of us (G. E. B.) gave excellent results.

REPORT OF CASES

CASE 1.—*Extensive synovial hemangioma; attempted excision and eventual amputation.*

E. E., a girl aged 8 years, was admitted to the hospital in December 1915 because of swelling of the left knee, which had been present since the age of 13 months. It was intermittent and at times painful. The family and past histories were irrelevant.

There was bluish mottling of the skin, extending from the left buttock down the side of the leg to the ankle. The left knee was swollen, but there were no other signs.

The knee was explored, and the entire joint cavity found to be filled with a mass of engorged, very thin-walled vessels. An attempt to dissect these free was accompanied by profuse and practically uncontrollable hemorrhage. A tourniquet was applied, and it was necessary to keep the tourniquet on the leg so long that permanent paralysis developed as a result of pressure on the sciatic nerve. Infection developed immediately after the operation.

After a stormy convalescence the infection subsided, but there was a remarkable amount of edema in the leg, with complete motor and sensory loss. No muscle power or sensation was regained below the knee. The child left the hospital with a healthy, granulating and oozing wound and wearing a posterior splint.

Several years later gangrene of the leg developed, for which amputation was necessary.

CASE 2.—*Extensive synovial hemangioma treated with radium.*

M. W., a girl aged 12 years, was admitted to the hospital on July 3, 1929, because of pain and swelling in the knee. She had been first seen at the age of 8 years, when treatment by rest was advised. She returned four years later, still complaining of a painful, swollen left knee. The swelling had not progressed in size but was more painful when the patient was going down stairs. The family and past histories were irrelevant. When the patient was 4 years old her mother noticed an intermittent swelling of the left knee. When this was present there was inability to flex the knee. It had gradually become more painful in the past year, especially during damp weather. There was an occasional sensation of locking in the knee.

Physical examination showed swelling on either side of the patellar tendon, floating patella, thickened synovia, limitation of motion, atrophy of the thigh and calf of the leg and shortening of the right leg to the extent of 0.5 cm. The roentgen findings were negative.

At operation the swelling, just lateral to the patella, was incised, the wall of a bluish gray sac being exposed. A considerable amount of free bleeding was encountered, and reddish, beadlike shiny bits of tissue filled the opening. A free tie was placed around a small mass of tissue and a section removed. The tissue taken for biopsy proved to be that of a hemangioma.

The patient left the hospital in good condition and was given radium treatment. At the time of the present report she has been under observation for eight years. There has been no recurrence.

CASE 3.—*Subsynovial pedunculated hemangioma yielding to easy excision.*

P. M., a boy aged 13, was admitted to the hospital in June 1930 because of pain in the right knee. The family and the past history were irrelevant. Five years previously there had been slight redness and swelling of the right knee, associated occasionally with some pain and stiffness. These symptoms never lasted more than three days. For three years the boy was observed and treated with rest.

The right knee was slightly enlarged over the lateral aspect. There were slight tenderness over the patella, extending to its lateral aspect, and slight restriction of motion, caused by muscle spasm.

At operation a pinkish tissue traversed by dilated tortuous vessels in the subsynovial tissue was exposed. It measured 4 by .2 cm. and was attached to the synovial membrane, merging down to the fibrous tissue at the edge of the external semilunar cartilage. It was removed in toto, with little bleeding.

The wound healed immediately, and the patient was discharged with the leg in a cast.

Up to the present time (six years later) the patient has remained free from symptoms, with no evidence of recurrence.

CASE 4.—*Extensive hemangioma of capsule and synovia treated with roentgen rays.*

M. K., a girl aged 6 years, was admitted to the hospital on Feb. 11, 1935, because of pain and swelling in the left knee, of six years' duration. The family and past histories were noncontributory. At the age of 5 months, when
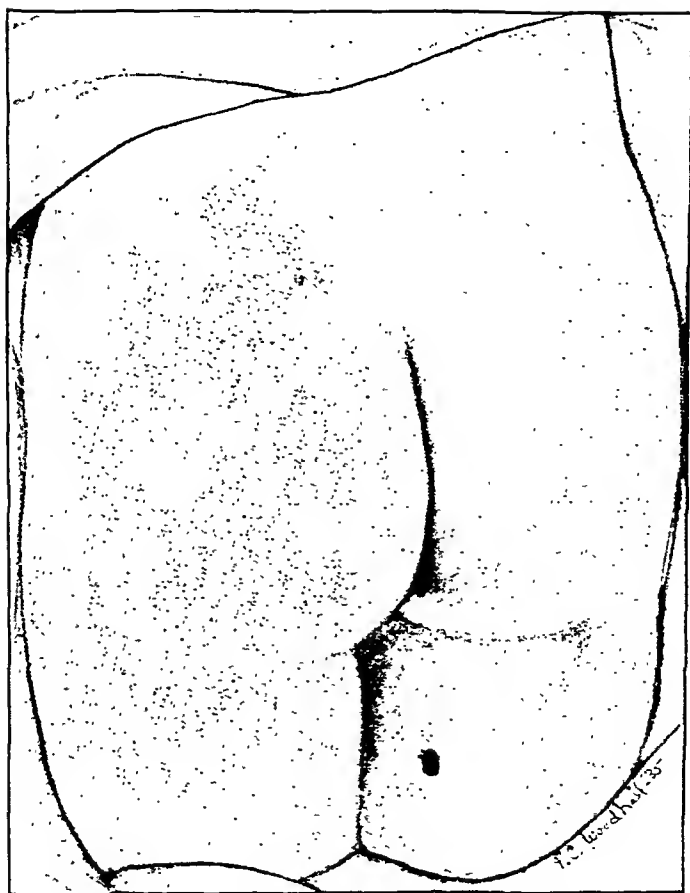
Fig. 1 (case 4).—Hemangioma of the buttock.

the patient attempted to stand the left leg was "drawn." There was a slight
increase in local heat about the knee with definite tenderness on palpation and
pain on motion. The condition was treated as a "strain" by the family physician,
who applied elastic bandages or rests for the recurrent attacks of pain and swelling.
These attacks occurred from three to six months apart. During one of them the
patient said she felt a "click" in the joint.

A large bluish discoloration was present over the lateral surface of the left
buttock and the upper part of the thigh, which showed an elevated, irregular
surface, soft and spongy to palpation. The left knee was swollen. The
swelling was localized on either side of the patella and for a distance of 6 cm.
above it. This swelling disappeared on elevation of the extremity but recurred
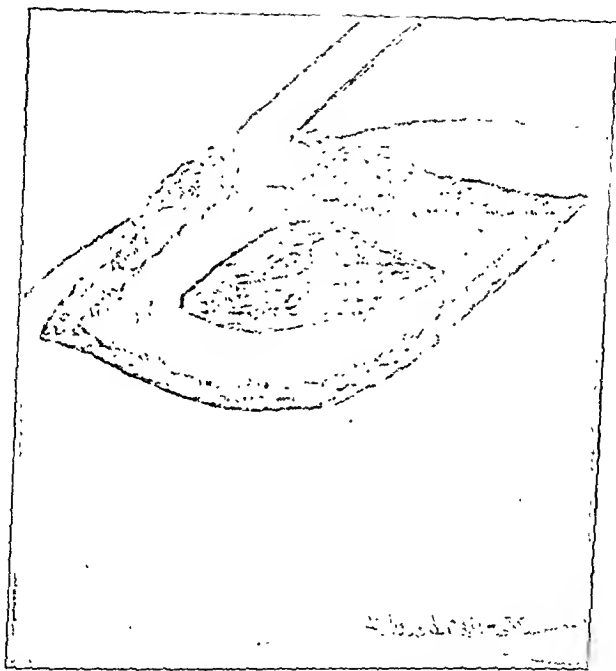
Fig. 2 (case 4).—Wormlike, thin-walled serpentinous vessels involving the
capsule of the joint, as seen at operation.

when the leg was put in a dependent position. There was a faint increase in local
heat, and the skin on the knee showed a bluish tint. On palpation there was no
tenderness, but there was a soft, almost fluctuant sensation. Slight limitation of
motion on extreme flexion was noted. Laboratory studies gave negative results.
A roentgenogram of the knee showed no abnormality, but a roentgenogram of
the thigh showed large, irregular shadows just beneath the skin. Nothing was seen,
however, which could be called a phlebolith.

At operation a longitudinal incision was made on the medial side of the patella
and carefully carried down through the skin and subcutaneous tissue. Just under-
lying this, in what seemed to be a capsule, there were wormlike, thin-walled,

knotty, serpentinous bluish vessels (fig. 2). A small tear was made into such a vessel. A number of hemostats were required to control the profuse hemorrhage. By careful dissection it was found that this hemangiomatous tissue extended into the quadriceps muscle. The wound was closed without the taking of a specimen for biopsy. A posterior splint was applied to the leg for two weeks. Healing occurred per primam intentionem.

Roentgen therapy was decided on, and the patient was referred to the Howard A. Kelly Hospital, Baltimore, for treatment. Up to the time of this report she has remained free from symptoms. The knee has returned to practically normal
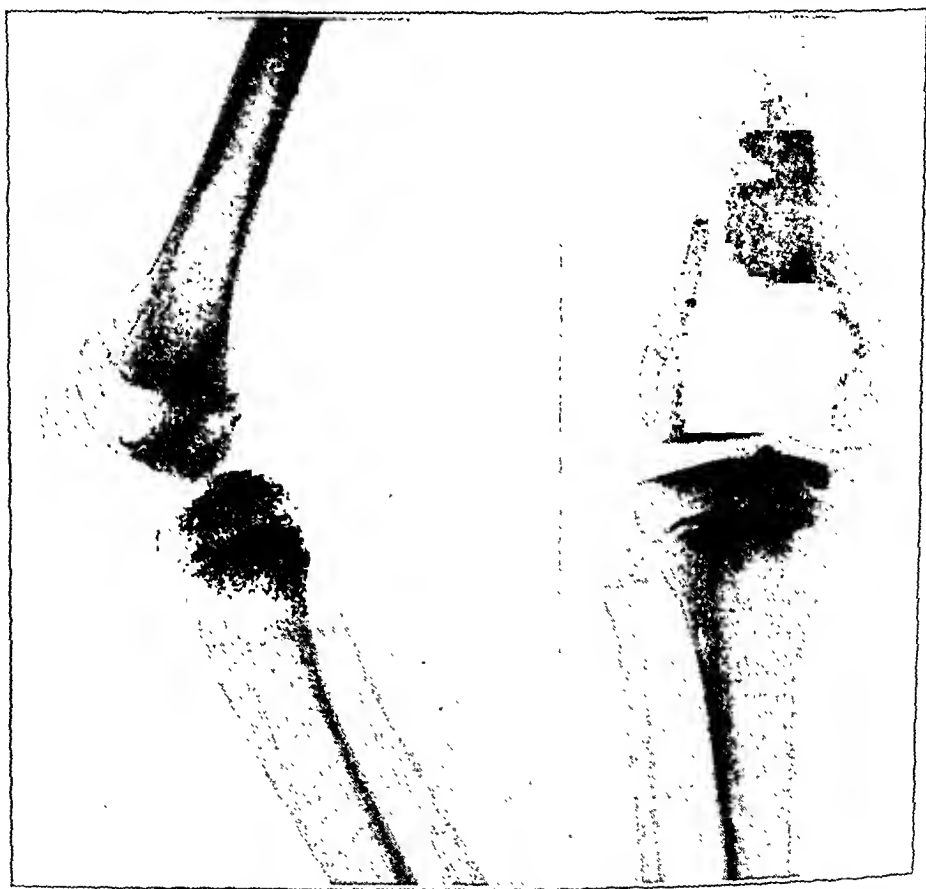
Fig. 3 (case 4).—Roentgenogram showing erosion of the cartilage and of the tibia and the femur at the capsular attachments.

size, but there are considerable contractures of the hemangiomatous tissue about the joint and slight erosion of the femur and tibia at the insertions of the capsule (fig. 3).

CASE 5.—*Hemangioma treated with roentgen rays.*

J. E. T., a youth aged 18, was admitted to the hospital on Jan. 5, 1937, because of swelling, a sensation of numbness and pain in the right knee on weight bearing, of ninety minutes' duration. The past and the family history were noncontributory.

There was a marked increase of fluid in the joint but no tenderness, relaxation of the joint, inflammatory signs or symptoms or signs of injury. A roentgenogram

disclosed only floating of the patella, indicating increased fluid in the joint. Pure blood was aspirated from the joint. This blood was not clotted or thinned. All laboratory examinations gave negative results.

The joint was explored elsewhere, and a quantity of liquid blood was obtained, which was without clot and more viscous than normal. No mass was found. No postoperative bleeding was encountered.

Subsequent examination showed that the swelling was still present. For this the patient was given high voltage roentgen therapy to a total of 3,200 roentgens. The knee definitely decreased in size until the patient was entirely well and free from symptoms, with normal, painless motion of the joint.

A brief synopsis of our series (table 1) reveals that there were 3 girls and 2 boys. The age at onset varied from eighteen months to eighteen years and the duration of symptoms from ninety minutes to eight years. Trauma was not a factor. Swelling was present in all cases, with pain and recurring attacks of limp and pain on motion in 4. The palpable elastic, spongy mass, compressible and distensible, was evident in only 2. There was tenderness in 2. Muscular atrophy and crepitation were present in only 1 case. Two of the patients received no treatment before operation, 2 were treated with rest in bed, and 1 was treated with bandages and casts. The roentgenograms throughout failed to show any abnormality except for erosion of the cartilage in case 4. In the first case complete excision was attempted, hemorrhage and infection followed, and finally amputation had to be performed. Complete excision was possible in only 1 case, in which the tumor was pedunculated. Biopsy followed by radium or roentgen therapy was carried out in the other 3 cases, with practically complete recovery. The final diagnosis of hemangioma was made and verified by histologic study in the first 4 cases. The signs, symptoms and course made the diagnosis certain in the last case.

REVIEW OF LITERATURE

Twenty-four authentic cases (table 2) of hemangioma of the knee joint, Weaver[1] included a third case, reported by Eve,[2] which in our opinion is not a proved case. A summary of the cases reveals that the age of onset of the symptoms varied from birth to 28 years of age; 85 per cent of the patients were under 16 years of age. However, when final treatment was instituted they varied from 10 to 37 years of age, and 90 per cent were over 16.

The duration of symptoms varied from one to twenty-five years. Trauma (some minor injury) was noted in 60 per cent, while in the

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1. Weaver, J. B.: Hemangiomata of the Lower Extremities, with Special Reference to Those of the Knee-Joint Capsule and the Phenomenon of Spontaneous Obliteration, J. Bone & Joint Surg. **20**:731-749 (July) 1938.

2. Eve, F.: Cases of Angioma of the Synovial Membranes and of Muscle, Brit. M. J. **1**:1143-1144, 1903.

TABLE 1.—Five Personally Observed Cases of Hemangioma of the Knee Joint

Patient	Date Seen	Sex of Patient	Age at Operation	Duration of Symptoms	Trauma	Pain and Swelling	Intermittent Symptoms	Tenderness	Elastic Spongy Mass	Distensible and Compressible	Pain on Motion	Limitation of Motion	Crepitation	Muscular Atrophy	Limp	Roentgen Examination	Preoperative Diagnosis	Preoperative Treatment	Treatment	Tissues Involved	Hemorrhage at Operation	Result
1. E. E.	1915	F	8	7	No	Yes	Yes	....	Yes	....	....	....	....	Yes	Yes	No abnormality	....	None	Attempted excision	Synovia	Profuse	Amputation
2. M. W.	1925	F	12	8	No	Yes	Yes	....	Yes	....	....	Yes	....	Yes	Yes	No abnormality	....	Rest in bed	Biopsy; radium therapy	Capsule and synovia	Moderate	Recovery
3. P. M.	1930	M	13	5	No	Yes	Yes	....	Yes	Yes	Yes	Yes	....	Yes	Yes	No abnormality	....	Rest in bed	Complete excision (pedunculated)	Synovia	None	Recovery
4. M. K.	1935	F	6	6	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	Yes	*Slight erosion femur and tibia	Heman-gioma	Bandages and cast	Biopsy; roentgen therapy	Synovia	Moderate	Recovery
5. J. T.	1937	M	18	30 min.	No	Yes	....	....	Yes	Yes	....	Yes	....	Yes	No abnormality	Heman-gioma	Aspiration blood	Explora-tion; roent-gen therapy	Synovia	Joint full of blood	Recovery

* When the patient was first seen the roentgenograms showed no abnormality.

other cases there was no history of injury. There were 13 male and 11 female patients. Pain and swelling, whether localized to one part of the joint or to the entire joint and the surrounding bursae, were constant symptoms. The history was that of recurring attacks with usually enough pain on motion to cause a limp. While tenderness was not a constant sign, an elastic, palpable spongy mass, compressible and distensible, disappearing on elevation of the extremity, was present in 70 per cent of cases. Atrophy of muscle was noted in 11 cases.

Most of the patients had been treated previous to diagnosis and operation by means of rest, hot or cold compresses, heat, massage, splints or casts. Eight of the 24 patients had been treated by aspiration of the joint, and in 7 of the 8 cases blood was aspirated. No preoperative diagnosis was made in 9 cases. Tuberculosis of the joint or synovial membrane was the diagnosis in 9 cases, while tumor, tumor of the cartilage, free body in the joint, torn semilunar cartilage, lipoma, syphilis and "encapsulated bloody joint effusion" were diagnoses made in the other cases. In only 1 case was the correct preoperative diagnosis made. Roentgenograms were of little help. Capsular thickening and vague shadows in the joints were seen in many cases. In 2, actual destruction of bone was evident. Treatment in all cases consisted of attempted excision of the tumor. Only in the cases in which a pedunculated, encapsulated tumor or a small synovial or capsular lesion was present was complete excision possible. In 6 of the 24 cases a second operation was necessary to remove the major part of the tumor and to control hemorrhage. Complete excision of the joint was necessary in 1 case, in which the tumor involved the patella, the tibia and the femur. In the majority of cases the involvement was limited to the synovia, the capsule and the subpatellar fat pad, with an occasional spread to the muscles of the lower part of the thigh. At operation the capsule was usually stained from the increase in venous blood. A mass was present, which appeared to be elastic, bluish and often glistening and to be made up of extremely friable, thin-walled vessels. When this mass was punctured, hemorrhage was always profuse and extremely difficult to control. At times the tourniquet and cautery seemed inadequate to keep the patient from bleeding to death during or after the operation, but no patient died, and complete recovery was reported in 11 cases. A good result, with 75 to 90 degrees of motion in flexion, was obtained in 7 cases. In 2 cases both extension and flexion was limited, and in the other there was a solid fusion of the joint. Recurrence was not noted in any case. The pathologic sections revealed hemangioma in every case. The histologic picture was typical of cavernous hemangioma, presenting irregular, blood-filled areas separated by serpentinous spongy thin tissue septums.

TABLE 2.—*Twenty Cases of Hemangioma of the Knee Joint Reported in the Literature*

Author	Sex of Patient	Age at Operation, Yr.	Duration of Symptoms, Yr.	Trauma	Pain and Swelling	Intermittent Symptoms	Tenderness	Elastic Spongy Mass	Distensible and Compressible	Pain on Motion	Limitation of Motion	Crepitation	Muscular Atrophy	Limp	Roentgen Examination	Preoperative Diagnosis	Preoperative Treatment	Operation	Tissues Involved	Hemorrhage at Operation	Result
Bouchut[16]	F	3	...	...	...	...	...	Yes	Yes	...	...	...	...	...	...	...	Aspirated blood	Died of diarrhea before operation	At autopsy, capsule and medial femoral condyle	...	Death (diagnosis verified by microscopic study)
Dudn[15a]	M	18	4 wks.	...	Yes	...	...	Yes	Yes	Yes	...	...	...	...	...	...	...	Complete excision	Capsule and ...	...	Recovery
Eve[2]	F	15	4	No	Yes	Yes	...	Yes	Yes	Yes	...	...	...	...	...	...	None	Partial excision	Capsule and synovia	Profuse	Recovery
Evo[2]	M	10	5	No	Yes	Yes	...	Yes	Yes	Yes	Yes	...	...	...	...	Tuberculosis	None	Complete excision	Capsule and vastus lateralis	None	Recovery
Zesas, D. G.: Deutsche Zts-chr. f. Chir. 82: 267-270, 1906	M	25	1	No	Yes	Yes	...	Yes	Yes	Yes	Yes	Yes	...	...	...	Tuberculosis	None	Complete excision	Capsule	None	Recovery
Reichel, P., and Nauwerck, C.: Arch. f. klin. Chir. 95: 890-902, 1911	M	18	2	No	Yes	Yes	...	Yes	Yes	Yes	...	...	...	...	...	Tuberculosis	None	Complete excision	Capsule and synovia	Moderate	Recovery 90° flexion
Seidener, M.: Dissert, Munich, 1910; Kastner and Culle, 1910	M	37	2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	...	...	Yes	Yes Capsular thickening	Tuberculosis or free body	Aspiration; phenol instilled; splint for 8 weeks	Complete excision	Synovia	None	Recovery 75° flexion
Müller[18]	F	17	2	No	Yes	Yes	Yes	Yes	Yes	Yes	...	...	Yes	Yes	Shadows under patella	...	Aspiration; rest; cast	Partial excision	Fascia, capsule and synovia	Profuse	Recovery
Oeser[11]	M	33	20	Yes	Yes	Yes	...	...	Yes	...	Yes	...	...	...	Essentially irrelevant	Tuberculosis	Bandage and massage	Complete excision	Capsule	Apparently none	Apparently Recovery
Osgood[12]	F	26	8	Yes	Yes	Yes	Yes	...	...	Yes	Yes	...	Yes	Yes	Atrophy of bone	Gumma, tumor, lipoma or tuberculosis	Periods of rest	Complete excision (pedunculated)	Synovia	Profuse	Recovery 90° flexion
Hügenberg, F. C.: Beitr. z. klin. Chir. 123: 645-654, 1921	M	19	5	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	...	Yes	Yes	Diffuse shadows in joint space	Tuberculosis	Rest; cast, 6 weeks	Complete excision	Synovia and infrapatellar fat pad	None	Recovery
																	Rest 4 weeks	Complete excision	Capsule; synovia; cartilage of lateral tibial condyle	Profuse	Partial recovery; 90° flexion

Reference	Sex	Age									Destruction	Diagnosis	Casts for first 5 years	2 operations; excision; arthrodesis	Capsule; tibia; femur; patella	Profuse	Solid fusion; no recurrence
Ilias[10]	M	23 30	25	No	Yes	Yes	Yes	...	Yes	Yes	Destruction medial tibial condyle	....	Rest	2 operations; excision; arthrodesis	Capsule; tibia; femur; patella	Profuse	Solid fusion; no recurrence
Ilias[10]	F	17 20	17	No	Yes	Yes	Yes	...	Yes	Yes	No abnormality	Hemangioma	Rest	2 operations; complete excision	Synovia	Mild	Recovery
O'Ferrall[14b]	M	19	6	Yes	Yes	Yes	Yes	...	Yes	...	No abnormality	Cartilage	Aspiration of blood; ice bandage	Complete excision	Capsule and synovia	Profuse; 2 operations to control bleeding	25° permanent flexion deformity; 105° motion
O'Ferrall[14b]	F	20 18	18	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No abnormality	Tumor of cartilage or tuberculosis	Cast and rest	2 operations; partial excision	Synovia and periosteum of femur	Profuse; controlled with pressure	Recovery; 105° flexion
O'Ferrall[14b]	F	21	10	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Shadows under patella	Lipoma	Ice cap and rest	Complete excision	Infrapatellar fat pad	None	Recovery
O'Ferrall[14b]	F	27	12	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Thickened periosteum end of femur	Tuberculosis	Heat; diathermy; rest	Complete excision	Patella, articular surface and capsule	None	Recovery
Bertelmann[20]	F	18	9	No	Yes	...	Yes	Yes	Yes	...	No abnormality	Encapsulated effusion	Aspirated blood	Complete excision	Synovia; capsule; femur	Profuse; controlled with pressure	Recovery
Eggers[4a]	F	30	2	Yes	Yes	...	...	Yes	Yes	...	No abnormality	....	Compression bandage and massage, 2 years	Partial excision	Synovia; entire crural space	Profuse	Symptom free for 1 year after operation
Lanwers, G. B.: Nederl. Tijdschr. v. geneesk. 22: 634 (Dec. 20) 1928	M	5	18 mo.	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	....	Aspiration 1 cc. blood	Partial	Synovia and capsule	Profuse	Marked limitation of motion
Venezian, E.: Chir. d. org. di movimento 14: 266-281 (Oct.) 1929	M	30	20	No	Yes	Yes	...	Yes	Yes	Yes	No abnormality	....	Heat, massage and casts for 10 years	Complete excision	Synovia	None	Recovery; 90° flexion
Bastos, E. S.: Bol. Soc. de med. e cir. de São Paulo 15: 175-178 (Feb.-March) 1932	M	19	10	Yes	Yes	...	...	Yes	Yes	Yes	Atrophy of bone	Tuberculosis, syphilis or internal cartilage	Bed rest for tuberculosis	Complete excision	Capsule; 2 cm. lobule	None	Recovery
Macmontell, P.: Bull. et mem. Soc. d. chirurgiens de Paris 28: 106-116 (March) 1936	M	29	17	Yes	Yes	Yes	Yes	...	Yes	...	Shadows above patella and phlebolites	Tumor	Aspiration of blood; rest	Complete excision	Synovia and capsule	Profuse	Recovery 1 month later
Mizuno, I.: Zentralbl. f. Chir. 61: 353-359 (Feb. 6) 1937	F	15	10	Yes	Yes	Yes	Yes	...	Yes	...	....	....	Plaster cast	Complete excision	Capsule; small encapsulated tumor	....	Recovery
Weaver[1]																	

CAUSE

The cause of hemangioma is still much discussed. The lesion is generally considered to be either congenital or traumatic. In about half the cases the patients report some minor injury, such as bumping the knee on closing a drawer or falling and striking the knee. However, in many cases no history of injury is obtained. The relatively early appearance of the tumor and its close association with telangiectasis and various other types of hemangioma as found in the skin,[3] muscle,[4] spine,[5] tendon sheaths,[6] and other structures of the body suggests a congenital origin. Jenkins and Delaney [7] in discussing various types of hemangioma stated:

It seems fair to assume as a working hypothesis that none of these vascular tumors are true growths and are due to faulty development, and that the variations encountered are due to the stage of vascular development in which deviation from the normal occurred.

Cases have been reported in which a cavernous hemangioma following trauma became malignant, metastases occurring in the skin of the head and in the skull.[8] So far, no malignant change in a hemangioma of the knee joint has been reported, and no such change, as far as can be determined, has occurred in any of our cases. The fact that hemangioma is seen most commonly in those parts [9] which in embryonic life correspond to fissures, the fact that a number of these articular tumors have arisen from the bones above and below the joint, the fact that the onset occurs before the patient begins to walk much or is able to injure the joint severely and the fact that the tumor is composed of immaturely formed blood vessels lead one strongly toward belief in a congenital origin.[10]

3. Roesler, H.: Hemangioma: Some Observations on the Results of Radiation Therapy, Am. J. Roentgenol. **27**:249-256 (Feb.) 1932.

4. (*a*) Eggers, H.: Zirkumskripte kavernöse Hämangiome der Kniegelenkskapsel, Zentralbl. f. Chir. **54**:1409-1411 (June 4) 1927. (*b*) Thomas, H. B.: Angiomas of the Skeletal Muscle: Combined Operative and Radiation Therapy; Two Case Reports, Am. J. Surg. **31**:354-360 (Feb.) 1936.

5. Heaney, F. S., and Whitaker, P. H.: Hemangioma of the Spine, Brit. M. J. **2**:775-776 (Oct. 28) 1933.

6. Burman, M. S., and Milgram, J. E.: Hemangioma of the Tendon and Tendon Sheath, Surg., Gynec. & Obst. **50**:397-406 (Feb.) 1930.

7. Jenkins, H. P., and Delaney, P. A.: Benign Angiomatous Tumors of the Skeletal Muscles, Surg., Gynec. & Obst. **55**:464-480 (Oct.) 1932.

8. Downing, J. G., and Mallory, G. K.: Cavernous Hemangioma and Trauma: Report of a Case, Arch. Dermat. & Syph. **22**:414-422 (Sept.) 1930.

9. Davis, J. S., and Wilgis, H. E.: Treatment of Hemangiomata by Excision, South. M. J. **27**:283-290 (April) 1934.

10. Haas, A.: Ueber Gefässtumoren der Kniegelenkkapsel, Deutsche Ztschr. f. Chir. **173**:130-141, 1922.

PATHOLOGIC PICTURE

This tumor has been studied minutely for its individual pathologic picture and is easily recognized as a pathologic entity. The capsule shows villous formation with deposition of blood pigment. The tumor is composed grossly of large masses of bluish venous sinuses interlaced on themselves, the individual sinus varying from the size of a small venule to more than 1 cm. in diameter. These are separated from each other by thin-walled, friable, partly fatty and partly connective tissue.[11] Microscopically [12] they are thin-walled vascular areas, varying greatly in size and showing much connective tissue cell proliferation. Because they do not carry the normal histologic coats of the true vessel walls, they cannot be thought to be varicose vessels or aneurysms. They are apparently neoplastic outgrowths of vascular tissue. The irregular spaces are lined with epithelium, the outer wall of the vessel usually being absent. A considerable amount of loose connective tissue containing blood vessels is seen all through the mass. Blood cells can be seen pushing their way between the lines of endothelial cells going to form new channels.

SYMPTOMS

All the cases present the same striking cardinal signs. They are pain and intermittent swelling since early life, with slight limitation on extremes of motion. The swelling, which is present about the patella, disappears on elevation of the extremity. There is no marked increase in local heat and usually no cutaneous discoloration. The swelling is boggy, almost fluctuant. Occasionally there is a clicking sensation in the knee. Pain is never constant but is occasionally associated with the swelling. Motion of the joint is usually free and painless.

EXAMINATION AND DIAGNOSIS

Tuberculin and Wassermann tests give negative results, and abnormal changes in the leukocyte count are not found. Roentgen examination generally shows only the swollen outlines of the joint; it discloses no changes in bone except occasionally atrophy of disuse or a slight erosion. Several authors [13] have reported the value of the appearance of phlebo-

11. Oeser, R.: Zur Kenntnis der Gutartigen Gelenkkapselgeschwülste. Beitr. z. klin. Chir. **107**:65-75, 1917.

12. (*a*) Duda, O.: Ueber einen Fall von Angiom der Kniegelenkkapsel, Greifswald, J. Abel, 1894. (*b*) Osgood, R. B.: Angioma of the Knee Joint, S. Clin. North America **1**:681 (June) 1921. Eve.[2] Haas.[10]

13. Teller, W. H.; Solis-Cohen, L., and Levine, S.: Cavernous Hemangioma of the Leg, Radiology **22**:369-371 (March) 1934. Davis, J. S., and Kitlowski, E. A.: Primary Intramuscular Hemangiomas of Striated Muscle. Arch. Surg. **20**:39-86 (Jan.) 1930. Eve.[2] Jenkins and Delaney.[7] Davis and Wilgis.[9]

liths in the roentgenogram not only as a diagnostic point but as a means of operative approach to the feeding vessels. Aspiration of the joint has been recommended and should be carried out in order to make the diagnosis certain.[14]   Visualization by radio-opaque substances offers a possible diagnostic approach.[15]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is important.   Hemangioma should not be confused with tuberculosis of the knee.   Note should be taken of the intermittent character of the swelling, the pain and the limp and also of the gradual increase in size of the swelling and of the doughy, knotty feeling on either side of the patella.   Also, if the condition is hemangioma the mass is reduced if the extremity is raised, the Mantoux test gives a negative result and roentgen examination does not reveal the signs of tuberculosis.   Syphilis of the joint may be ruled out by a negative reaction to the Wassermann test and absence of the other signs of congenital syphilis.   Syphilis does not present a compressible mass or free blood in the joint.   Traumatic effusion usually causes a more symmetric swelling and outlines the bursae.   In the presence of such effusion there is true fluctuation and may be change in surface temperature and greater pain on motion.   The swelling is noncompressible, and serous or serosanguineous fluid may be aspirated.   The history of an occasional locking or clicking sensation may lead to the diagnosis of injury to the semilunar cartilage, but the feeling of the mass about the patella, the history of long duration and the change in size of the mass on elevation of the leg will make the diagnosis clear.   An infectious lesion shows more pain on motion, increase in local heat, extremely acute recurrence of symptoms, persistent swelling and possible involvement of other joints or roentgenographic changes in the bones.   Xanthomatous villous arthritis of the knee (a rare condition) will confuse the diagnois more than any other condition.   However, a chemical study of the cholesterol content of the blood and synovial fluid will aid materially in differentiating the two conditions.

14. (a) Bouchut, E.: Tumeur érectile de l'articulation du genou, Gaz. d. hôp. **29**:379, 1856. (b) O'Ferrall, J. T.: Hemangiomas of the Knee Joint, J. A. M. A. **85**:505-508 (Aug. 15) 1925. Osgood.[12b] Roesler.[3]

15. (a) Patey, D. H.; Tatham, R. C., and Nicholas, F. G.: The Use of X-Rays in the Investigation of Varicose Veins, Lancet **2**:1309-1311 (Dec. 9) 1933. (b) Otell, L. S.; Coe, F. O., and Hedley, O. F.: Thorotrast Arteriography and Veinography, M. Ann. District of Columbia **2**:153-156 (July) 1933. (c) Allen, E. V., and Barker, W. W.: Roentgenologic Visualization of the Veins of the Extremities: Preliminary Description of a Method, Proc. Staff Meet., Mayo Clin. **9**:71-74 (Jan. 31) 1934.

TREATMENT

Since this lesion appears so early in life, it would seem that the earlier the treatment the more satisfactory the result. The tumor may take one of three forms: diffuse, pedunculated or encapsulated. In any case it will remain stationary, regress in size or grow very rapidly at any time or age of the patient, seemingly regardless of the presence or absence of competent cause.[16]

The type of treatment is a matter of choice. Hemangioma in general has been treated by excision or by conversion of the mass into scar tissue, solid carbon dioxide, sclerosing solutions, roentgen and/or radium radiation,[4b] or the cautery being used. In general, the type of tumor indicates the type of treatment. For hemangioma of the knee joint, treatment by excision has been carried out in almost all the cases reported. This procedure is excellent for the small impinging hemangioma [12b] or for the occasional pedunculated hemangioma,[17] which can be easily stripped away from the surrounding tissue, tied and removed. For the large wormlike sinus formation leading far up into the muscle or down into the periosteum, cartilage or bone [18] the chances of complete excision are not great. Each writer has reported the difficulty of controlling hemorrhage from the bone and the extensively involved capsule. Some surgeons have used many ligatures; others have used pads of fat over the bleeding vessels, and still others have found a second operation necessary to control hemorrhage.[10] Complete excision is a difficult matter,[19] and cases of recurrence have been reported. In 1, removal of the ends of the femur and tibia and fusion of the joint were necessary [10] both to control hemorrhage and to insure complete excision and relief of symptoms. Infection followed by gangrene and amputation was the result in 1 case. However, many cases have been reported in which complete removal of the hemangioma was followed by healing per primam intentionem and by complete relief of symptoms. These cases demonstrate the guarded prognosis as to the range of motion that will be obtained after operation and as to the freedom from symptoms.[19] There is no doubt that a large hemangioma of muscle, skin, tendon and subcutaneous tissue can be removed surgically with good results.[8] Surgical treatment in our first case resulted finally in the loss of the extremity; in the third the lesion was pedunculated and could easily be removed; in the second case a specimen was taken for biopsy and subse-

16. Traub, E. F.: Should Vascular Nevi Be Treated? Arch. Pediat. **50**:272-278 (April) 1933.

17. Oeser.[11] Jenkins and Delaney.[7]

18. Müller, W.: Beiträge zur Kenntnis des Lymphangioms, Beitr. z. klin. Chir. **84**:511-536, 1913. Duda.[12a] Oeser.[11] Osgood.[12b]

19. Osgood.[12b] Haas.[10]

quent radium treatment given, and in the fourth and fifth cases exploration only was attempted and the patient referred for roentgen therapy. In our third case the lesion apparently healed completely, and the patient has been free from symptoms for years after treatment, without clinical signs of recurrence of the tumor. Owing to the operative dangers and the uncertainty of the operative results, complete removal was not attempted in our 3 cases,[20] roentgen therapy being preferred. This was first suggested in 1925 but was not attempted prior to the cases reported in this paper so far as we know.

CONCLUSIONS

The cardinal points in the diagnosis of hemangioma are (1) intermittent pain and swelling present since early life, with or without history of trauma, (2) no pain on motion, (3) slight limitation of motion, (4) the presence of another hemangioma anywhere on the body, (5) reduction in size of the swelling on elevation of the extremity, (6) negative results from laboratory and roentgen examinations and (7) aspiration of blood from the joint.

For the small or pedunculated tumor the treatment is complete excision. Owing to the almost uncontrollable hemorrhage, with the danger of loss of function of the joint, amputation or infection followed by septicemia we believe that a larger nonpedunculated tumor is more satisfactorily treated by rest and by radium or roentgen therapy.

20. Bertelsmann, R.: Zirkumskripte kavernöse Hämangiome der Kniegelenkskapsel, Zentralbl. f. Chir. **54**:710-711 (March 19) 1927. Patey and others.[15a]

ATRESIA ANI URETHRALIS

REPORT OF A CASE

L. ALBERT THUNIG, M.D.
BROOKLYN

"Congenital malformations of the rectum and anus are rare. Various authors give the incidence of 1 in 5,000 to 1 in 10,000. No two lesions seem to be identical in their physical characteristics, though fundamentally they are all variations of a known embryonic plan of development." [1]

These figures refer to all types of anal and rectal anomalies. The incidence of the particular anomaly to be described in this paper is considerably smaller, as it comprises less than 30 per cent of the incidence of all anomalies of the rectum and anus. That this is so and that the operative mortality rate is high and the failure to accomplish a satisfactory result common are borne out in statements quoted by Young.[2]

Cripps [3] collected 100 cases of imperforate anus. There were 13 male patients, of whom 10 died. Autopsy was performed on these. Six had fistulas between the prostate and the rectum; 4, had fistulas between the rectum and the bladder.

Keith [4] among 114 cases found 33 in which there was a communication between the rectum and the urethra.

Quinland [5] reported 27 cases of imperforate anus; there were 7 male patients, 6 of whom had urethrorectal fistulas.

Barney [6] among 375 cases found 94 in which the rectum communicated with some part of the urinary tract.

Ladd and Gross [7] among 162 anomalies of the anus and rectum found only 9 in which the rectum communicated with the urethra.

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1. David, V. C.: Surgery of the Rectum and Anus, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 7, chap. 6, p. 1.

2. Young, H.: Congenital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937, pp. 580-583.

3. Cripps: St. Barth. Hosp. Rep. 18:65, 1882.

4. Keith, A.: Brit. M. J. 2:1736, 1908.

5. Quinland, W. S.: Boston M. & S. J. 187:870, 1922.

6. Barney, J. D.: Tr. Am. A. Genito-Urin. Surgeons 21:393, 1928.

7. Ladd, W. E., and Gross, R. E.: Am. J. Surg. 23:167, 1934.

OPERATIVE PROCEDURES AND RESULTS

Colostomy was proposed by Littre in 1710.[8] Bell of England in 1787 made the first perineal dissection.[6] Campbell of the United States in 1790 performed the first successful perineal operation.[6] In 1828 Dieffenbach proposed the perineal operation.[9]

In a series of 55 cases of atresia ani urethralis occurring in males, reported by Parin,[8] the immediate operative mortality was 32 per cent. In only 1 case was a perineal rectal plastic operation with attempt to close the urethral fistula performed; the patient in this case died. In 4 cases perineal rectal plastic operations were performed with secondary closure of the urethral fistula; there was 1 death.

In 9 cases of atresia ani urethralis reported by Ladd and Gross[7] the combined operation of perineal rectal plastic procedure and closure of the urethral fistula in one stage was performed on 7 patients; 4 died, 3 recovered, and there was only 1 cure. In 2 cases the urethral fistula was operated on when the patient was 5 years old, with 1 cure and 1 failure. As a result of their experience Ladd and Gross have decided that the method of choice is immediate colostomy with a perineal plastic operation when the patient is 8 or 9 years old.

Young[9] stated that two schools have developed: (1) physicians favoring a primary colostomy with secondary perineal repair, and (2) physicians favoring an immediate perineal plastic operation.

I feel justified in placing my case on record in view of the following facts:

1. The anomaly to be reported is rare.

2. The operation was undertaken ·forty-eight hours after the child was born.

3. The procedure was a primary perineal plastic operation with attempt to obliterate the fistula between the urethra and the rectum.

4. The operation resulted in recovery with a very good anus, and good function was apparent during eleven years of observation.

I feel justified, furthermore, in devoting space to a description of the embryonic background of this anomaly and a correlation between the embryologic facts and the anatomic conditions found at operation in addition to that devoted to facts evidenced by function, for the reason that I believe that only by such detailed attention to these anomalies will physicians eventually be able to discard conjecture and come to fairly accurate conclusions as regards the factors of developmental error producing these interesting anomalies.

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8. Parin, B.:   Arch. f. klin. Chir. **166**:386, 1931.
9. Young,[2] p. 581.

REPORT OF CASE

R. F., a boy born Sept. 2, 1925, was an apparently robust baby weighing about 8 pounds (3,628 Gm.). He had normal male genitals with testes in the scrotum and a normal attachment of the umbilical cord (also, a normal umbilicus after separation of the cord). There was some vomiting during the second day; the baby voided urine normally but had no stool. When the child was about 40 hours old, the nurse, in starting to give an enema, found no evidence of an anus and also noticed that the boy was passing very dark urine. Examination showed that the boy was passing meconium through the penis, and inspection of the anal area showed a perfectly flat surface without even a dimple where the anus should have been. The baby was removed to the Swedish Hospital.

An F. 8 metal Gouley tunneled catheter was introduced, with the following results: 1. When the catheter was passed in the usual manner and the stilet withdrawn, almost clear urine was obtained (fig. 1). 2. When the catheter was passed with easy pressure of the curve of the instrument on the perineum,
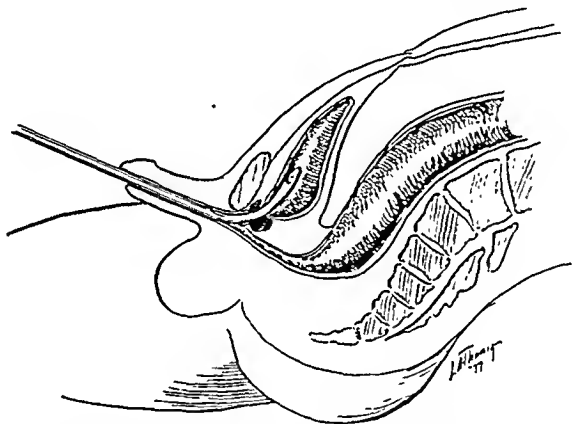
Fig. 1.—Semidiagrammatic drawing of the anomaly with an F. 8 Gouley tunneled catheter in position, the tip being in the bladder.

the tip pointing toward the sacrum, meconium came through the catheter on withdrawal of the stilet (fig. 2). 3. It was found that this procedure could be repeated at will with the greatest ease.

The three facts just mentioned established the following conclusions:

1. There was a communication between the urinary tract and the rectum.

2. This communication was between the urethra and the rectum, for it is obvious that if the opening had been in the bladder it could not have been found at will.

3. The communication was with the penile portion of the urethra. The ease of the procedure and the position of the metal catheter verified this fact, for if the point of communication had been in the membranous or the prostatic portion of the urethra the technic of passing the catheter would have been different, and the procedure certainly would not have been so easy.

4. There was not merely an opening but a definite tract between the penile portion of the urethra and the blind end of the rectum, and the rectum was not

attached immediately to the proximal end of the penile portion of the urethra. The depth to which the catheter had to be passed to obtain meconium showed that the rectal pouch was some distance from the proximal end of the urethra and was close to the sacrum. (This was confirmed at operation.) (Figure 2 is drawn to show the position of the catheter when it was being passed and not the depth to which it could be passed. Had I drawn the catheter well into the rectal pouch, the point which I wished to demonstrate, i. e., the technic of passing, would have been lost.)

5. Some part of the rectum was present moderately low in the pelvis.

6. The bladder, which functioned apparently normally, was not involved in the anomaly.

With the preoperative diagnosis well established, operation was performed on September 4, the boy being about 48 hours old. Owing to the fact that this baby was returned home immediately after operation, the records of the Swedish Hospital show only the schedule for the operation; all facts given here are from my private records.
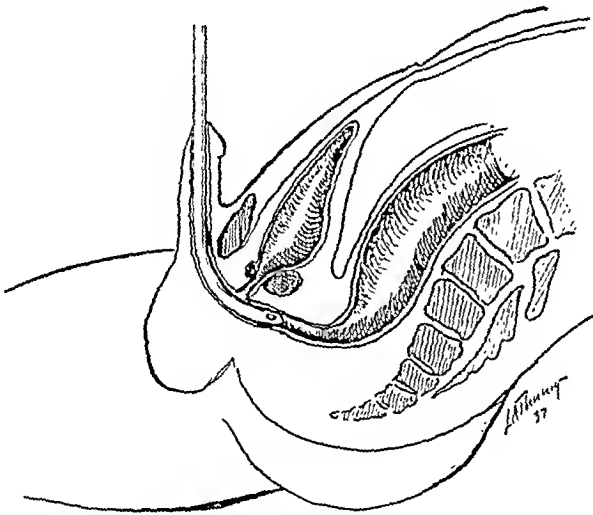
Fig. 2.—Semidiagrammatic drawing of the anomaly with an F. 8 Gouley tunneled catheter in position, the tip being in the tract between the rectum and the urethra. The catheter is shown in this position to demonstrate the position of the instrument which is necessary to avoid the membranous portion of the urethra and to assure entrance into the rectum.

Operation.—The operation was performed without anesthesia. The baby was held in the lithotomy position with the thighs flexed on the abdomen and the scrotum well forward. A metal F. 8 Gouley tunneled catheter was passed through the penile portion of the urethra and fistulous tract into the rectal pouch. This instrument was held steadily in the midline by Dr. J. Borgia. A median perineal incision was made from just behind the scrotal perineal junction to within a short distance of the coccyx. There was no external evidence of a sphincter muscle, but I believed that if the muscle were present its fibers might be split by keeping directly in the midline. After the cutaneous incision had been made, no attempt was made to find the sphincter, but midline dissection was done. Sharp and blunt dissection was carried slowly upward, the curve of the sacrum being followed and the catheter guide being avoided to prevent vesical or urethral damage. At a distance of 1½ to 2 inches (3.7 to 5 cm.) above the perineal level the dark rectal pouch was seen. Exploratory aspiration was

made with a fine hypodermic needle, and meconium was obtained. Two heavy black silk sutures were then placed in the walls of the rectal pouch as guides and tractors. By blunt dissection this pouch was mobilized from the sacrum, care being taken to avoid the peritoneum anteriorly. Without difficulty the pouch was freed so that without tension it could be delivered well below the perineal level. The tract between the rectum and the bladder was ligated with two ligatures, the metal catheter having been withdrawn some time previously, close to the rectal pouch to avoid "Y-ing" the urethra and ligating the same; it was then cut between the ligatures. The rectal pouch was now drawn about 1 inch (2.5 cm.) below the perineal level and was opened with an anteroposterior median incision which gave two fairly large lateral flaps. This incision was followed by a most copious meconium stool. No attempt was made to obtain a cutaneous rectal suture line for the reason that this might be followed by rectal retraction with serious or fatal consequences. Instead, the lateral flaps were brought well over the line of the cutaneous incision on each side and sutured with several heavy black silk sutures to the unbroken skin. The idea underlying this procedure was that the raw rectal surface would come into contact with the whole thickness of incised skin, connective tissue and sphincter muscle (if this was present); it would furthermore allow for rectal retraction, which could easily take place by cutting through of the silk sutures and still give some rectal edge outside the pelvis. It would also allow for some sloughing of the rectal edge without interference in cutaneous rectal union. The remaining ends of the perineal cutaneous incision were then brought together with interrupted sutures. The operation took about one and one-quarter hours.

The immediate postoperative course was uneventful. There was no infection. The child nursed well; there was no more vomiting and the bowels functioned. The redundant rectal tissue retracted somewhat and sloughed somewhat, and a very presentable anus developed. At times the skin became red and irritated, but function was excellent. Control at this time was difficult to interpret. For the first few months the parents kept the anus well dilated by daily passage of a 4LF rubber rectal bougie, and I frequently examined and dilated it with my finger.

For two years continued improvement took place, with apparently good rectal and excellent vesical control. At the cutaneous rectal edge, however, a small urinary fistula developed, through which with the act of urination some urine occasionally leaked, and very rarely a trace of feces appeared in the urine by way of the urethra. The follow-up demonstrated that the presence of this trace of feces was not due to any rectal-urinary fistula but to the forcing of feces into the open end of the penile portion of the urethra at the perineal-anal junction during defecation or cleansing; this fecal contamination was then washed out in the act of urination. By Dec. 3, 1927, the boy was having fair-sized, formed stools under control; feces appeared in the voided urine only when a saline laxative was given. By September 1929 control of the bowel was excellent; control of the bladder was perfect, with only an occasional perineal urinary leak with voiding. By March 1932 there were no traces of feces in the voided urine and only occasionally was there a urinary leak on urination. This boy was last seen Jan. 6, 1936. He was having fair-sized, well controlled formed stools with absolutely no rectal leakage unless he had been given a saline laxative, in which case the leakage was only slight. He still had a small urethral-perineal fistula, which opened near the anus, but there was no more contamination of the urine with traces of feces.

The reader will probably wonder why I have not reported the physical findings with the follow-up reports. I was unable to make rectal examinations even

though I was particularly anxious to do so; I had to depend entirely on the record of function and the size of the stools. It may be difficult to believe that the simple process of rectal examination should for any reason be withheld, but it was, for the following reasons: First, this boy was an excellent example of a spoiled child, as was his elder brother, through whose intolerable behavior during an illness in February 1936 my connection with this interesting case was severed. Second, the boy had a series of physical mishaps. In July 1927 he had mild ileocolitis; in June 1928 he had measles; in December he had lobar pneumonia; in January 1929 he had a severe infection of the upper part of the respiratory tract, with bilateral purulent otitis media; in January 1930 he had acute polyarthritis with early severe endocarditis and pulmonary infarct; in February he had recurrent otitis media; in March he had recurrent low grade arthritis with exacerbation of the endocarditis and severe decompensation, and in the same month he had severe chorea with increased endocarditis and decompensation, which made the outcome look very dubious until June. At the first recession of his trouble his tonsils were removed (in June). From June 1930 until January 1936 he had no more acute diseases but suffered with numerous attacks of decompensation. His heart was hugely dilated and hypertrophied, actually causing deformity of the left side of the chest. The liver was large and congested, with variable edema; in short, there was a chronic cardiac valvular lesion which might be expected to make a semi-invalid of the boy for the rest of his life. This series of infections superimposed on an inherited neurotic makeup and the indulgent attitude of the parents toward the boy will, I hope, make it clear that my failure to make rectal examinations was due to circumstances over which I had no control. As a result of his inheritance, environment and physical misfortunes this 11 year boy became absolutely unmanageable in the presence of a physician. At the time of writing he attends a special class for children with cardiac disease and gets along well, his anal condition causing him no annoyance whatever and the occasional urinary leak only slight annoyance, none if he sits down when urinating, to which he seriously objects. In view of the slight inconvenience of this perineal urethral fistula and of the fact that there is no contamination of the urinary tract with feces I advised the parents that it would be best to wait until the boy's general health was better and he had grown before attempting to correct this condition.

Summary.—This was a typical case of atresia ani urethralis or imperforate anus with communication between bowel and urethra, as it is now termed. In my opinion: "congenital absence of the anus with a persistent cloacal duct" is a better name, as both of the previous names predicate the presence of an anus, whereas in this case no anus was present. The term persistent cloacal duct (as will be shown later in this paper) both defines the anomaly and gives its origin.

The case was one in which forty-eight hours after birth a primary perineal rectal plastic operation was undertaken, which resulted in a functioning anus with almost total sphincter control and no tendency to stricture for at least eleven years. There was at no time any difficulty in emptying the bladder or controlling the flow.

The tract between the rectum and the urethra was severed, but at the end of eleven years a small fistula was present between the proximal end of the penile portion of the urethra and the perineum, just in front of the anus. This leaked slightly during urination only. Because the discomfort caused by this fistula was moderate and because the boy's general condition was poor, postponement of operation to correct the fistula to a later period was advised.

In addition to an unusual congenital anomaly operated on with good results the report presents eleven years of the medical history of a most unfortunate boy.

EMBRYOLOGY

In the following section the paragraphs are numbered so that quick reference may be made to them when desired.

1. In discussing the embryologic background I desire to bring forward those facts which relate particularly to the anomaly just presented, and in order to prevent confusion I shall avoid mentioning any association that these facts may have with closely related anomalies. It is my opinion that in attempting to point out with even a semblance of accuracy the factor or factors of developmental error leading to an anomaly it is essential to show not only the actual factor or factors of error but also to limit the cause of the anomaly to the suspected factors by demonstrating the absence of developmental error in organs or structures closely associated in embryonic life with the anomalous organs or structures. For that reason I shall attempt to show not only the actual developmental error but also the development of those anatomic parts which were found to be normal at birth but which were intimately associated with the anomalous parts in embryonic growth.

2. Before entering into the discussion I should like to explain my use of the words "modified copy," used frequently in the legends for the illustrations appearing in this paper. In figures 3 and 4 I have left out those parts of the original which have no bearing on the subject. In figure 14 *A* I have left out several parts already shown in figure 11, which have served their purpose. In all other instances in which drawings are not originals I have tried faithfully to copy the original; I have not made any anatomic changes but have modified my copy in the technic of artistic presentation only.

3. In order that the reader may associate the size of the embryo with the period of development, the following tabulation is quoted from Keith.[10]

Weeks	Millimeters
3	0.5
4	2.5
5	5.5
6	11.0
7	17.0
8	25.0

4. Figure 3 represents an embryo of 1.7 mm. The embryo proper is almost straight, and the yolk sac is proportionately very large with two early outgrowths from the yolk sac into the embryo, one at the

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10. Keith, A.: Human Embryology and Morphology, ed. 5, Baltimore, William Wood & Company, 1933, p. 62.
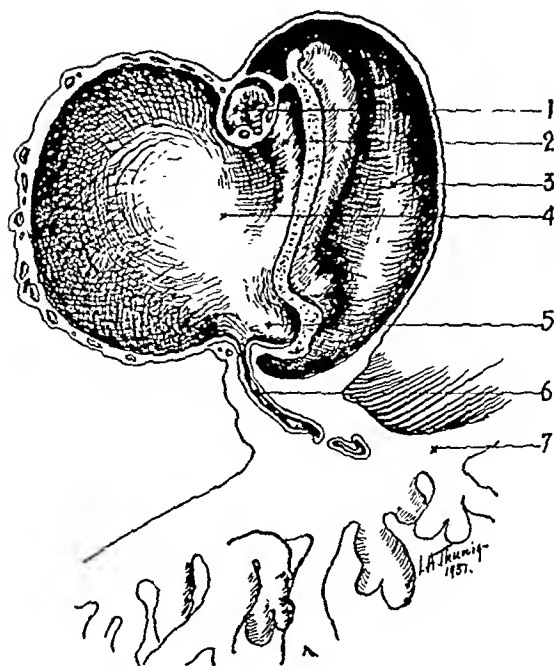
Fig. 3.—Drawing of a 1.7 mm. embryo: a modified copy of an illustration in Cullen, T. S.: The Umbilicus and Its Diseases, Philadelphia, W. B. Saunders Company, 1916, p. 2. *1*, heart; *2*, foregut; *3*, amniotic cavity; *4*, yolk sac; *5*, hindgut; *6*, allontois in body stalk; *7*, chorion.
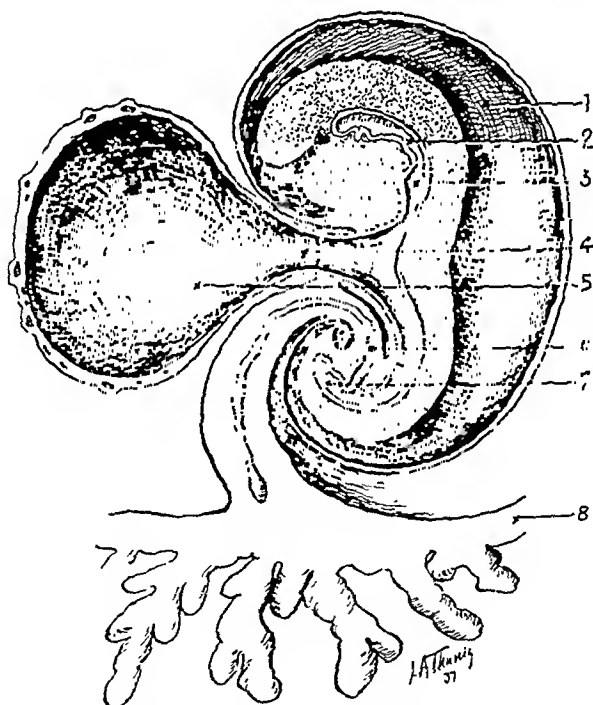
Fig. 4.—Drawing of a 2.5 mm. human embryo: a modified copy of an illustration in Cullen, T. S.: The Umbilicus and Its Diseases, Philadelphia, W. B. Saunders Company, p. 3. *1*, amniotic cavity; *2*, esophagus; *3*, stomach; *4*, omphalomesenteric or vitelline duct; *5*, yolk sac; *6*, allantois; *7*, cloaca; *8*, chorion.

cephalic and one at the caudal end; these become the foregut and the hindgut respectively. Even at this early stage the allantois is present, extending from the yolk sac near the hindgut into the body stem toward the chorion. As a matter of fact, the allantois has been demonstrated in embryos even before the hindgut or foregut could be demonstrated.[11]
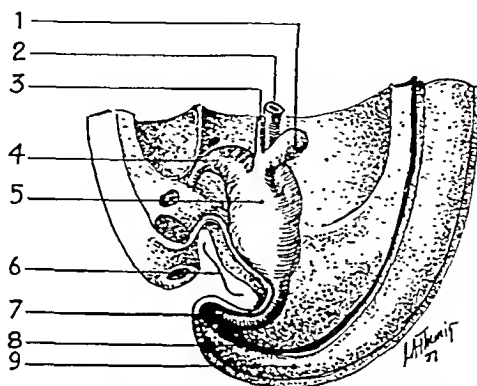
Fig. 5.—Model of a 6.5 mm. human embryo: (modified copy of an illustration in Bailey and Miller[16] [p. 370]): *1*, kidney bud or ureteral bud; *2*, hindgut; *3*, mesonephric or wolffian duct; *4*, urachus; *5*, cloaca; *6*, cloacal membrane; *7*, caudal gut; *8*, notochord; *9*, neural tube.
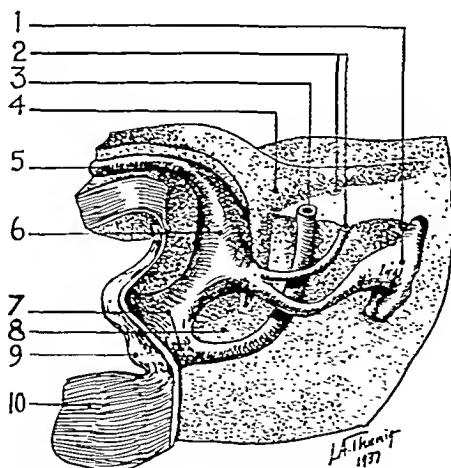
Fig. 6.—Reconstruction of the caudal end of a 11.5 mm. human embryo: (modified copy of an illustration in Bailey and Miller[16] [p. 372]): *1*, primitive renal pelvis; *2*, mesonephric or wolffian ducts; *3*, rectum; *4*, coelum; *5*, urachus; *6*, bladder; *7*, cloaca (undivided portion); *8*, site of urorectal fold; *9*, cloacal membrane; *10*, tail.

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11. Keibel, F., and Mall, F. P.: Manual of Human Embryology, Philadelphia. J. B. Lippincott Company, 1912, vol. 2, pp. 293-294.

The allantois [12] is carried along with the hindgut and empties into the terminal part of the hindgut or cloaca (fig. 4).

5. In the 4.9 mm. embryo the cloaca is elongated anteroposteriorly and the wolffian (primary excretory or mesonephric) ducts empty into its ventral portion.[13] In figure 5 the cloaca is shown in an embryo of 6.5 mm., and in addition to the wolffian ducts the kidney·buds or, according to Keibel and Mall, the ureteral buds, are present.[14] At this period the wolffian ducts enter the ventral portion of the cloaca laterally. Between the 5.3 mm. stage and the time the embryo has reached 15.5 mm. the cloaca is divided into two parts by a fold of tissue (fig. 6) known as the urorectal fold.[15] There is some difference of opinion as to the formation of the urorectal fold and since the anomaly under discussion depends largely on the division of the cloaca I have chosen to dwell long enough on this particular point to demonstrate at least two of the commonly accepted and outstanding views. Bailey and Miller [16] stated the opinion that the urorectal fold is formed by paired folds arising on the lateral walls of the cloaca at its cephalic end, which spread downward and unite to form a single septum which divides the cloaca (figs. 7 and 8) into an anterior part, the urogenital sinus, and a posterior smaller part, the rectum.[16] Keibel and Mall described the urorectal fold as an unpaired fold starting in saddle fashion at the cephalic end of the cloaca, between the allantois and the hindgut, and gradually projecting downward, growing somewhat faster at the lateral walls than at the center, thus giving the free lower edge of the fold a curved rather than a straight edge. They maintained this view on the ground that no raphe is formed as would be the case if two lateral folds came together and fused centrally and also on the ground that Keith [10] in 1896 described a groove or slight ridge on the outer surface of the cloaca (fig. 9) corresponding with the line along which this unpaired fold grew internally.[15] These authors also stated that epithelial differentiation between the rectum and the ventral remains of the cloaca (fig. 10) takes place before the actual division of the cloaca.[15] About the time the embryo has reached 11 to 12.5 mm. the urorectal fold (figs. 9 B and 9 C) has divided the cloaca so far caudally [17] that only a duct remains between the rectum and the urogenital sinus, the so-called cloacal duct. At 15 mm. the cloaca is still not fully divided. At 15.5 mm. (approximately 7 weeks) the cloaca is just divided but the epithelium of the

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12. Keibel and Mall,[11] p. 294.

13. Keibel and Mall,[11] pp. 314 and 322.

14. Keibel and Mall,[11] p. 834.

15. Keibel and Mall,[11] p. 871.

16. Bailey, F. R., and Miller, A. M.: Text-Book of Embryology, ed. 5. Baltimore, William Wood & Company, 1929, p. 370.

17. Keibel and Mall,[11] pp. 322 and 872.
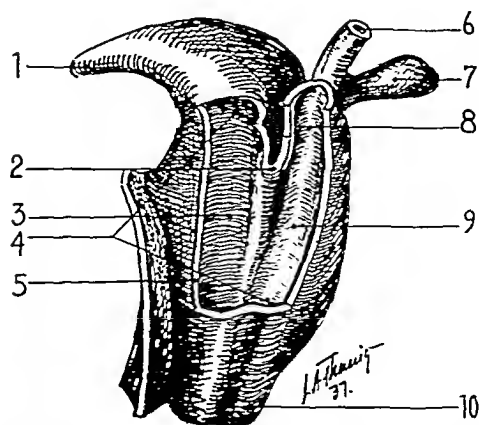
Fig. 7.—Model of the cloacal region in an embryo slightly older than that shown in figure 5: (modified copy of an illustration in Bailey and Miller [16] [p. 371]): *1*, urachus; *2*, urorectal fold; *3*, urogenital sinus: *4*, cloaca; *5*, cloacal membrane (laterally); *6*, mesonephric or wolffian duct; *7*, kidney or ureteral bud; *8*, intestine (hindgut); *9*, rectum. *10*, caudal gut.
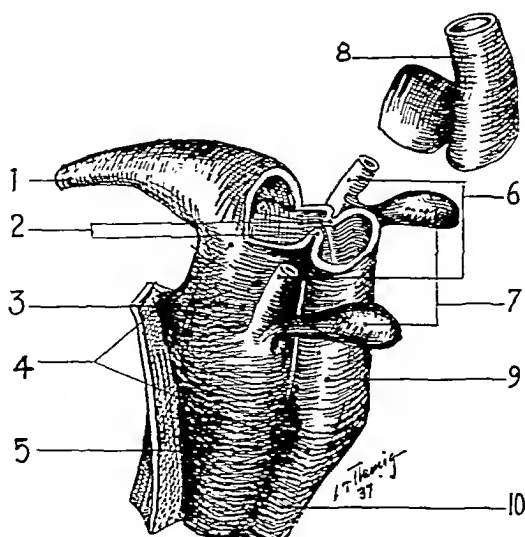
Fig. 8.—Reconstruction drawing of the cloaca, based on figure 7 and statements in the text and schematically sectioned to demonstrate the two lateral folds: *1*, urachus; *2*, urorectal folds; *3*, urogenital sinus (wall); *4*, cloaca (wall); *5*, cloacal membrane (laterally); *6*, mesonephric or wolffian ducts; *7*, kidney or ureteral buds; *8*, intestine (hindgut); *9*, rectum (wall); *10*, caudal gut.
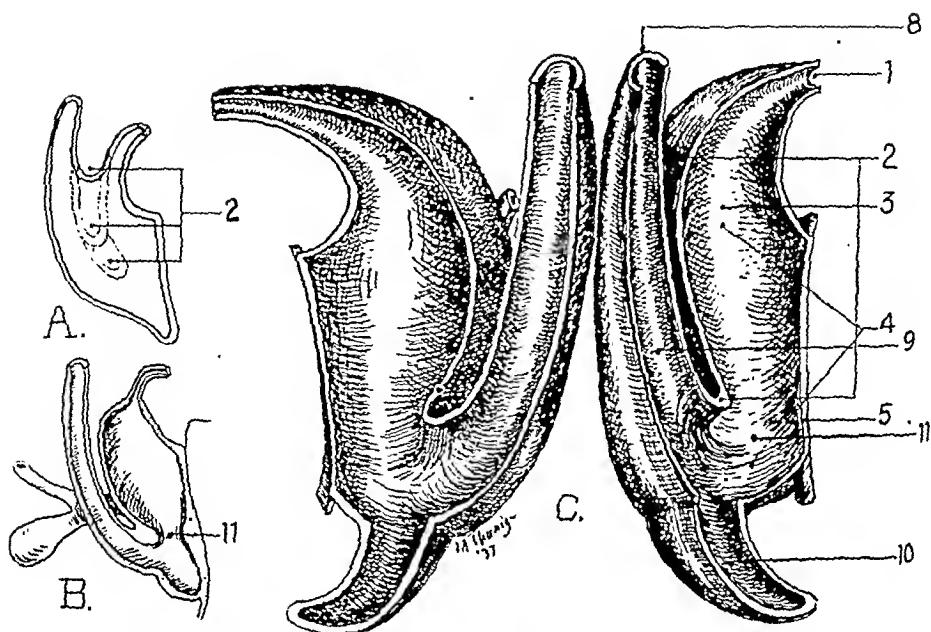
Fig. 9.—A, drawing of a model of the cloaca in a 7 mm. embryo in which the separation of the cloaca by an unpaired urorectal fold from above is shown diagrammatically (copied from an illustration in Keibel and Mall[11] [vol. 2, p. 872]). B, drawing of a model of a 7 mm. embryo, showing a sagittal section of the cloaca (copied from an illustration in Keibel and Mall[11] [vol. 2, p. 873]). C, schematic drawing (original) based on A and B and conforming for comparative reasons with figure 7 and figure 8. For purposes of demonstration the right half of the cloaca has been turned backward and is accordingly foreshortened. The parts are numbered as in figures 7 and 8: 1, urachus; 2, urorectal fold or (saddle); 3, urogenital sinus; 4, cloaca (undivided portion); 5, cloacal membrane (ventrally); 6, mesonephric ducts, hidden from view; 7, kidney or ureteral buds, hidden; 8, intestine (hindgut); 9, rectum; 10, caudal gut; 11, cloacal duct of Reichel (1893).
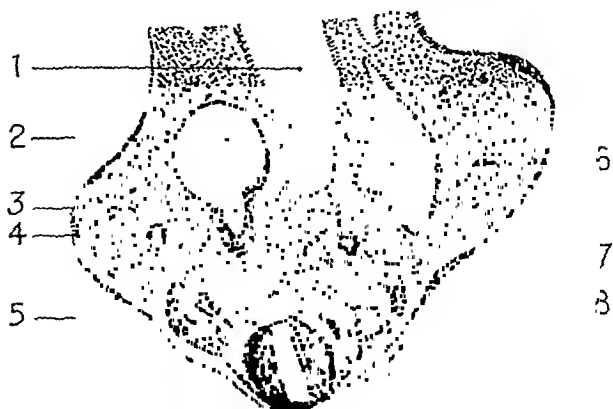
Fig. 10.—Drawing of a transverse section of a 4.7 mm. human embryo (copied from an illustration in Keibel and Mall[11] [vol. 2, p. 805]): 1, left umbilical artery; 2, urogenital portion of cloaca; 3, rectal portion of cloaca; 4, primary excretory mesonephric or wolffian duct; 5, twenty-sixth primitive segment; 6, coelum; 7, metanephrogenic tissue; 8, twenty-seventh primitive segment.

rectum and that of the urogenital sinus are still connected.[15] In other words, the cloacal membrane is still present. This leads to a discussion of the cloacal membrane. Before proceeding it may be well to recapitulate.

6. The allantois, mentioned in paragraph 4 as entering the cloaca, is now connected with the primitive bladder and the urogenital sinus by means of the urachus (originally the allantois). The ventral part of the cloaca (bladder and urogenital sinus) is now completely separated from the posterior part, the rectum down to the cloacal membrane.

7. The wolffian ducts and ureteral (or kidney) buds, last mentioned in paragraph 5, now show considerable advancement. The ureteral
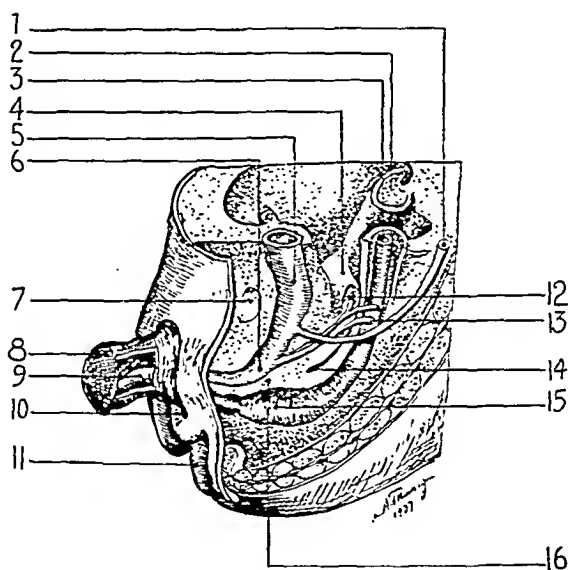
Fig. 11.—Reconstruction of the caudal end of a human embryo of 25 mm. (8½ to 9 weeks), one evidently destined to be a female, though the anatomic parts involved in the anomaly under discussion are still sexually undifferentiated (modified copy of an illustration in Bailey and Miller [16] [p. 372]): *1*, mesonephric or wolffian duct; *2*, genital gland or ovary; *3*, intestine; *4*, peritoneal fold (broad ligament); *5*, anlage for bladder; *6*, pars pelvina, urogenital sinus; *7*, symphysis; *8*, genital tubercle (phallus); *9*, pars phallica of urogenital sinus; *10*, anal membrane or anus; *11*, tail; *12*, müllerian duct; *13*, ureter; *14*, rectouterine excavation; *15*, rectum; *16*, urorectal fold.

[NOTE.—Embryologists refer to the primitive clitoris, as well as to the primitive penis, as the phallus.]

buds have grown backward, producing well defined ureters and renal pelves (fig. 6). At 10 to 14.5 mm. the terminal piece of the wolffian

18. Keibel and Mall,[11] p. 323.

duct on each side has been absorbed to form part of the bladder. The ureters and wolffian ducts open separately but close together in the vesicourethral portion of the urogenital sinus (fig. 11). The cranio-lateral migration of the ureters begins in the 13 mm. embryo. The wolffian ducts remain close together and at the same site at which they were; this site is to become Müller's hillock, which is to project into the urethra and form one of the points of the vesical trigon.[19] The
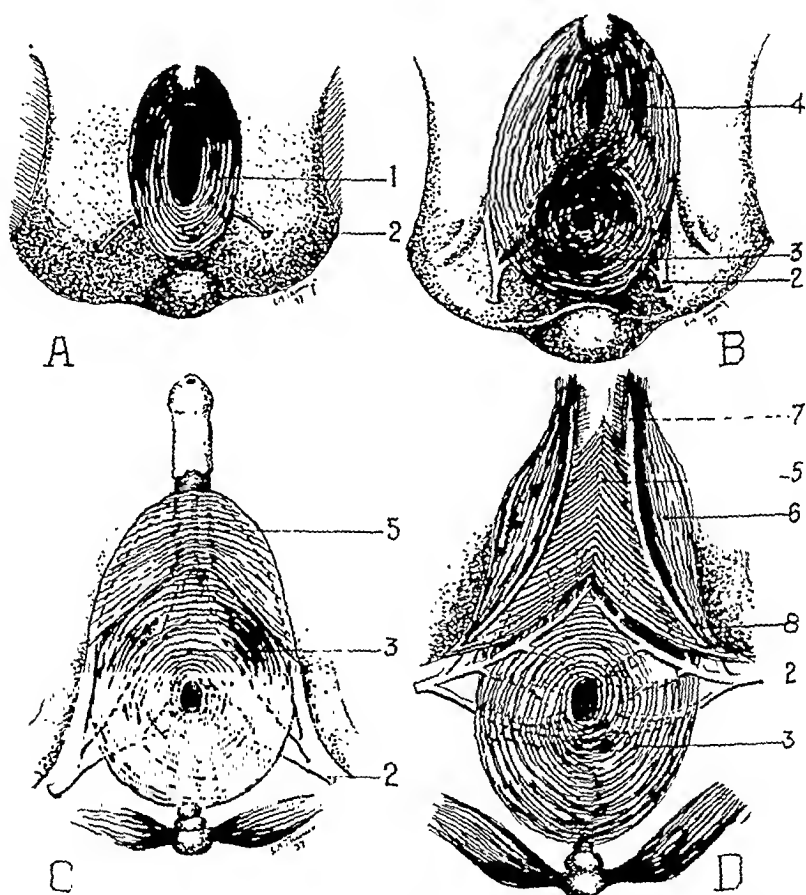
Fig. 12.—Muscles of the sexually indifferent and the male perineum. (These drawings were copied from an illustration in Keibel and Mall[11] [vol. 1, p. 479] reproduced from Popowsky, J.: Zur Entwickelungsgeschichte der Dammuskulatur beim Menschen, Anat. Hefte [Abt. 1], 1899, no. 38, p. 15, figs. 1, 2, 3 and 6). (*A*) an embryo of two months, (*B*) an embryo of three months, (*C*) a male fetus of four months and (*D*) a male fetus of five months: *1*, sphincter cloacae; *2*, pudendal nerve; *3*, sphincter ani externus; *4*, sphincter sinus urogenitalis; *5*, bulbocavernous muscle; *6*, ischiocavernous muscle; *7*, dorsal nerve of penis; *8*, nerve for ischiocavernous muscle.

caudal portions of the wolffian ducts become the vas deferens, and their ends in the urethra become the ejaculatory duct.[20]

19. Keibel and Mall,[11] pp. 877-878.
20. Bailey and Miller,[16] p. 386.

8. The rectum has now become independent and brings the hindgut down in direct continuity with that portion of the cloacal membrane now known as the anal membrane (figs. 11 and 15 *A*).

9. In order that the structure of the cloacal membrane (last mentioned in paragraph 5) may be understood, it is necessary to establish a few facts heretofore not mentioned in reference to the cloaca itself. The cloaca described in previous paragraphs is formed by entoderm, being derived directly from the hindgut. In addition to this entodermal cloaca, which, according to Keith, is the only part students of embryol-
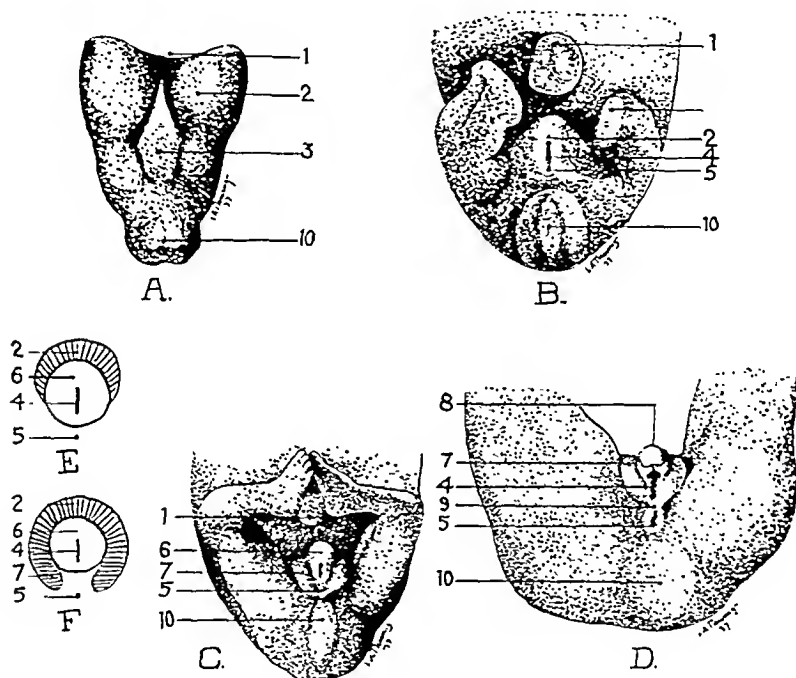
Fig. 13.—Development of external genitals in the male. *A*, model of the cloacal membrane of a human embryo of 3 mm. (copied from Keibel and Mall[11] [vol. 2, p. 872]). *B*, caudal end of a human embyro of 18 mm. *C*, indifferent external genitalia of an embryo of 28 mm. D, male external genitalia at 3½ months. (*B*, *C* and *D* are copied from photographs in Keibel and Mall[11] [vol. 2, pp. 947-950].) *E*, diagrammatic representation of the division of the cloacal tubercle into the phallus and the genital tubercle after Keibel and Mall[11] [vol. 2, p. 948]. *F*, diagrammatic representation of the formation of the genital swellings, based on figure 13 *E* and on text of Keibel and Mall.[11] Key to *A-F*: *1*, umbilicus; *2*, cloacal tubercle (paired in *A*); *3*, cloacal membrane; *4*, urogenital opening (present but not labeled in *C*); *5*, anal groove (*B*) anus (*C* and *D*); *6*, phallus; *7*, genital swelling (*C*); *8*, glans penis; *9*, unpaired scrotal area (see text); *10*, coccygeal tubercle.

ogy have in mind when they speak of the cloaca, there is a corresponding depression or sagittal groove (fig. 13) which is formed by ectoderm

and is known as the ectodermal cloaca.[21]   In the human embryo of
11 to 13 mm. there is an oval pit (ectodermal cloaca) extending from
the coccygeal prominence to the tip of the genital eminence.[22]   Unques-
tionably there is some misconception in the general conception of the
cloaca, and I believe this is due to the fact that one is accustomed to
consider the human embryologic cloaca in terms of the cloaca of ovi-
parous mammals or of birds.   That is, one looks on the embryonal cloaca
as an opening rather than as a closed sac.   With that conception in
mind it is difficult to visualize a cloacal membrane.   But if one bears
in mind [23] that the entodermal cloaca is a closed sac which is never
normally opened outside (into the amniotic cavity [22]) and that its ento-
dermal wall comes into contact with and fuses with the ectodermal wall
of the ectodermal cloaca, or groove, the formation of the cloacal mem-
brane is easy to comprehend (figs. 5, 6, 13 *A* and 16 *A*).   Some
embryologists have stated that the cloacal membrane consists of ento-
derm and ectoderm only, the mesoderm being pressed aside; others
have stated that there is also a thin layer of mesoderm.[24]

10. The cloacal membrane is now intact (paragraphs 6 and 8) with
the urorectal fold down to it.   The cloacal membrane now consists of a
urogenital membrane and a rectal membrane (figs. 15 *A* and 16 *A*).
By referring to figure 13 *A* one notes that there are two cloacal tubercles
(ectodermal) with the cloacal membrane between them forming a parti-
tion between the cavity of the entodermal cloaca and the groove of the
ectodermal cloaca.   In figure 13 *B* the cloacal tubercles have fused to
form a single cloacal tubercle, and on the anal slope one sees the ecto-
dermal cloaca with the urogenital opening and the anal groove.   In
figure 13 *C* the phallus is present, which develops and is seated on the
cloacal tubercle like a tower on a hill.[25]   At 22.8 mm. the area which
was originally urorectal fold [18] shows mesodermal growth, with the
development of a well marked primitive perineum; this is shown as
the area between the anal area and the urogenital area in figures 11,
13 *B*, 13 *C* and 16 *A*.   This primitive perineum is found at the bottom
of the ectodermal cloaca.   The anal membrane is also found in a
depression at the bottom of the ectodermal cloaca; this depression is
termed the anal pit or proctodeum (figs. 11, 13 *B* and 16 *A*).   While
these external changes have been taking place, internal changes have
been keeping pace with them, particularly in the urogenital sinus.   The
points at which the ureters and wolffian ducts open mark the boundary
between a slightly larger cephalic part of the urogenital sinus, the anlage

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21. Keith,[10] p. 431.   Keibel and Mall.[18]
22. Pohlman, A. G.:   J. Anat. **12**:5, 1911.
23. Keibel and Mall,[11] p. 870.
24. Keibel and Mall.[23]   Bailey and Miller.[16]
25. Keibel and Mall,[11] p. 948.
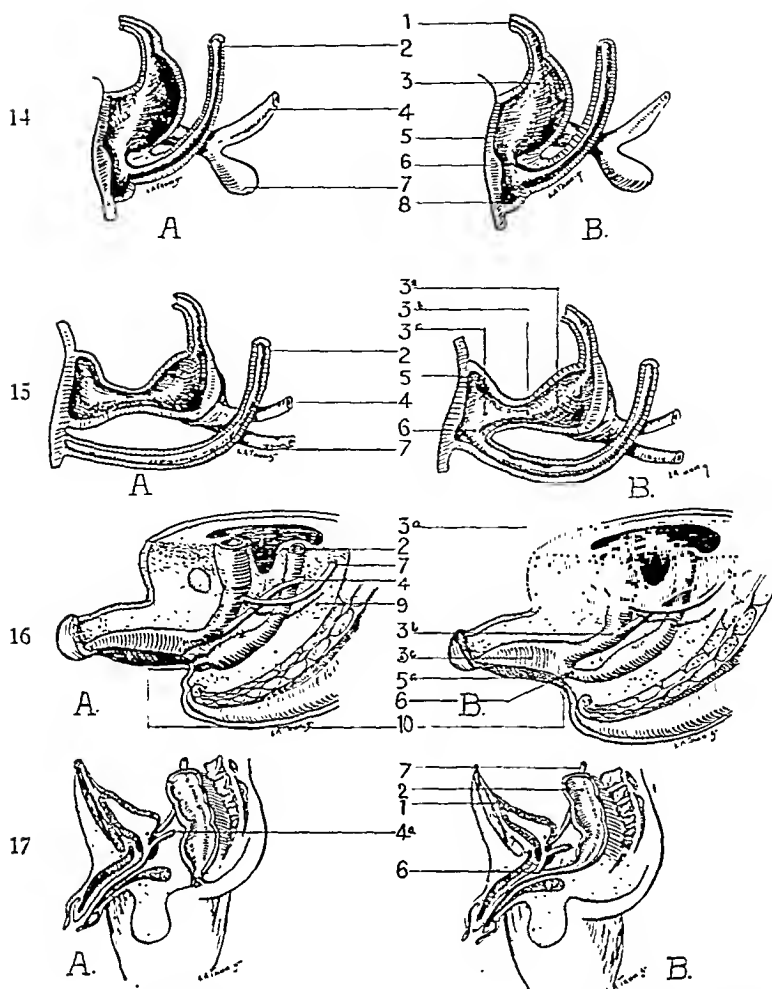
Fig. 14.—*A*, model of the normal cloaca of a 7 mm. embryo after Keibel and Mall [11] [vol. 2, p. 873]. *B*, model of the cloaca of a 7 mm. embryo. The text will show that up to this point the cloacal development in the anomaly was the same as in the normal.

Fig. 15.—*A*, model of the normal cloacal region of an 11 mm. embryo (copied from Keibel and Mall [11] [vol. 2, p. 874]). The rectum is completely separated from the urogenital sinus, which now shows three definite divisions. The caudal gut has disappeared. *B*, schematic drawing (original) of the anomalous clocaca. The urorectal fold has failed to separate the rectum from the urogenital sinus, and the cloacal duct persists.

Fig. 16.—*A*, drawing based on figure 11 and a drawing in Arey [29] [p. 146]. It is a reconstruction of the normal caudal end of a 25 mm. embryo. *B*, drawing showing the anomalous condition in development. The drawing is semidiagrammatic. The anal pit (proctodeum) and the entodermal anal membrane are missing. The persistent cloacal duct is now drawn out into a tract (see text).

Fig. 17.—*A*, semidiagrammatic representation of structures shown in figures 14 *A*, 15 *A* and 16 *A* as they appear at birth under normal conditions. *B*, semidiagrammatic representation of structures shown in figures 14 *B*, 15 *B* and 16 *B* as they were in the anomaly at birth. (See figs. 14, 15, 16 and 17). Key to *A* and *B*: *1*, urachus; *2*, rectum; *3*, urogenital sinus; *3a*, urogenital sinus— vesicourethral anlage; *3b*, urogenital sinus—pars pelvina; *3c*, urogenital sinus— pars phallica; *4*, mesonephric or wolffian or primary excretory duct; *4a*, meso- nephric duct, now ejaculatory duct and terminal end of vas deferens and tubules of epididymis; *5*, cloacal membrane; *5a*, urogenital membrane (cloacal membrane); *6*, cloacal duct; *7*, ureteral or kidney bud and ureter; *8*, caudal gut; *9*, mesentery of rectum; *10*, anal pit (*A*) and anal site (*B*).

(primordium, literally "beginning") of the bladder and a small caudal part [26] which becomes the urethra and urogenital sinus (figs. 11, 16 *A* and 17 *A*). After the bladder begins to enlarge, the adjacent part of the urogenital sinus becomes slightly constricted (figs. 6, 11, 15 *A* and 16 *A*). This marks the proximal end of the male urethra.[26] Keibel and Mall [27] described the cloacal remains as becoming divided into a wide dorsal portion and a ventral portion with a narrow middle portion (figs. 6, 11 and 15 A). From the posterior broad lumen the vesicourethral anlage is formed; the narrow part becomes the pars pelvina of the urogenital sinus and the broad ventral part the pars phallica of the sinus urogenitalis.[27] The pars pelvina is the actively growing part which pushes the pars phallica before it.[28] Some believe that as the phallus grows the urogenital sinus (pars phallica) is drawn out into it.[29]

11. The urogenital membrane [30] runs along the anal slope of the cloacal tubercle and later along the phallus, in which organ it becomes enclosed (figs. 11 and 16 *A*). The breaking through of the urogenital membrane and anal membrane takes place independently, forming the anal orifice and urogenital orifice.[31] Keibel and Mall stated that the breaking through takes place in embryos between 13 and 18 mm., the anal opening being formed somewhat later than the urogenital.[31] They also stated: [32] "The perforation of the anal membrane normally takes place in embryos of 30 mm." Also: "In the Harvard collection there are embryos measuring 22 mm., 22.8 mm., and 29 mm. in which perforation has occurred, and specimens of 22.8 mm. and 30 mm., in which the anus seems still impervious." Also: "Keibel and Elze's series of 7 embryos measuring 22 to 26 mm., includes only 1 (22.5 mm.) in which the anus is open." From these statements one must conclude that the anal perforation takes place considerably later than the urogenital perforation if one accepts 13 to 18 mm. as being correct for the perforation of the urogenital membrane. The urogenital membrane ruptures normally when the division of the cloaca is complete.[22]

12. The foregoing paragraphs have presented a description of the development of the anus and rectum apart from its mesentery, the musculature controlling the same and the pushing backward of the anus which is due to an enlargement of the urorectal fold [33] (primitive perineum, paragraph 10). To refer again to figure 13 *C*: The formation of

26. Bailey and Miller,[16] p. 371.
27. Keibel and Mall,[11] p. 876.
28. Keibel and Mall,[11] pp. 962-963.
29. Johnson, F. P.: J. Urol. 4:449, 1920.
30. Keibel and Mall.[27] Johnson.[29]
31. Keibel and Mall.[11] p. 872.
32. Keibel and Mall.[12] p. 324.
33. Bailey and Miller.[16] p. 394.

a phallus, referred to in paragraph 10, has divided the cloacal tubercle into a phallus and genital tubercle, as is shown diagrammatically in figure 13 *E*. The lateral growth of the genital tubercle as shown diagrammatically in figure 13 *F* has given rise to genital swellings as shown in figure 13 *C*. In figure 13 *D* the phallus has grown larger, and the glans penis is present. The glans is marked off in a 26 mm. embryo, and at three months the male phallus remains perpendicular to the body, and the female phallus bends downward.[34] Figure 13 *D* also shows the anus completed, with the urogenital sinus still open along the entire length of the phallus except the glans. That part of the urogenital sinus which is to form the glans portion of the urethra becomes perfectly solid and forms the urethral plate.[34] The urethral plate is eventually converted into the urethral groove and then closed over to form a tube [35] which becomes continuous with the phallic sinus urogenitalis, which by this time has also closed over, thus completing the entire penile portion of the urethra.[36] The prepuce is formed by an epithelial cylinder that grows in from the epithelium of the external surface of the glans penis.[36] In figure 13 *D* the genital swellings are seen to have become the scrotal swellings; the scrotum, however, with the descent of the testicles, is formed from that part designated in figure 13 *D* as the unpaired scrotal area into which the scrotal swellings extend. The scrotal swellings fade out into the surrounding areas.[37] According to Bailey and Miller [38] and Arey,[39] the scrotum is formed by fusion of the genital swellings, which fusion results in a raphe. When the raphe in the perineal region formed by the fusion of the ectodermal cloaca is present the permanent perineum is formed.[18] This raphe extends from the frenum of the prepuce to the anterior margin of the anus.[40]

13. With the exception of the muscles and the mesentery of the rectum the development of all embryonic structures closely related to the anomaly have been completed. I should like to add that the urachus finally becomes the middle umbilical ligament (fig. 17 *A*) and that the allantois, from which the urachus is derived, plays little part in the formation of the bladder, the bladder being formed almost wholly from the anterior part of the cloaca and from the inclusion of the bases of the wolffian ducts. If any part of the bladder is derived from the allantois, it is only the apex.[26]

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34. Keibel and Mall,[11] p. 949.

35. Keibel and Mall,[11] p. 964.

36. Keibel and Mall,[11] p. 955.

37. Keibel and Mall,[11] pp. 952-953.

38. Bailey and Miller,[16] p. 396.

39. Arey, L. B.: Developmental Anatomy, ed. 3, Philadelphia, W. B. Saunders Company, 1934, p. 164.

40. Keith,[10] p. 441.

14. The development of the muscles of the perineum can best be understood by referring to figure 12 and by quoting Keibel and Mall:[41]

Popowsky has given the best account of the development of the muscles of the perineum. They arise from the musculus sphincter cloacae, a skin muscle, which is present in the 2 months embryo [fig. 12 A]. During the third month of fetal life it divides into an M. sphincter ani externus and an M. sphincter sinus urogenitalis [fig. 12 B]. This division is dependent upon the separation of the single cloacal opening into two openings. The M. sphincter ani externus alters very little during the later development, but the M. sphincter sinus urogenitalis undergoes many changes, giving rise as it does to perineal muscles. During the fourth and fifth months the M. sphincter urogenitalis gives rise first to M. ischiocavernosus, M. bulbocavernosus and M. sphincter urethrae membranaceae. The M. transversus perinei are the last ones to develop out of the peripheral and lateral part of the M. bulbocavernosus. The M. levator ani arises from quite a different source and only secondarily comes into relation with the M. sphincter ani and the perineal muscles. The M. levator ani arises in connection with the M. coccygeus and gradually descends to the rectum, bladder, prostate and vagina and thus comes into contact and intimate union with the muscles of this region. The difference in the nerve supply between the perineal muscles and the M. levator ani indicates their different origin.

This conception is followed by Keith.[40] Jordan and Kindred, cited by Young,[42] and Arey[43] maintained that the cloacal sphincter muscle is derived from the third and fourth coccygeal myotomes. Young stated that Otis (1905) found that the development of the external sphincter ani produces characteristic elevations. In embryos of 21 to 23 mm. there is a pair of external elevations, one on either side of the anal pit. At 26 mm. these unite to make the posterior side of the anus, forming a crescentic mound (fig. 13 C). Finally the elevations meet anteriorly, encircling the anus.[44]

15. Regarding the internal sphincter ani, it has been stated that just before the rectum reaches the anal membrane it forms a bulbous enlargement (figs. 11 and 16 A). In embryos of 17.5 mm. and 18.5 mm. the circular and longitudinal muscle fibers are easily recognized. The terminal swelling of the rectum extends beyond the muscle layers (Keibel, 1896). Keibel and Mall[32] described the musculature in a 29 mm. embryo as follows:

The circular muscle layer ends very abruptly at the level of the little caudal swelling of the intestine, and already it may be referred to as the beginning of the muscle sphincter ani internus. The outer longitudinal layer of the intestinal musculature is arranged differently. It ends at the same level, but no sharp caudal limit can be recognized. The M. sphincter ani externus is clearly indicated and is relatively quite large. The cranial border of this muscle is found

41. Keibel and Mall,[11] pp. 478-480.
42. Young,[2] p. 576.
43. Arey,[20] p. 227.
44. Young,[2] p. 579. Keibel and Mall.[32]

where the musculature of the intestine ends, therefore at the level of the little caudal entodermal enlargement. The M. sphincter ani externus is separated from the epithelium of the intestine by a rather thin layer of connective tissue, which is continuous with the connective tissue surrounding the intestine further cranially, and also with the longitudinal layer of the muscularis, from which strands of cells may be followed into it.

16. In my opinion the peritoneum is also a factor in the anomaly under discussion, not as a causative factor but as an important modifier of the anatomic relations of the structures involved in the anomaly. Almost as soon as the mesoderm is formed it splits into two parts. The space between these two parts becomes the coelum and the inner layer joins with the entoderm and forms the primitive mesenteries. The lower part of the gastrointestinal tract, or hindgut, has only a posterior mesentery.[45]

Previous to the middle of the fourth month, the gut is freely movable within the scope of its restraining mesentery but soon secondary adhesions occur which attach certain segments. The ascending colon and descending colon are applied against the body wall on the right and left sides respectively.[46]

Keith[47] stated: "The adhesions as they form, contract and thus draw the various parts of the alimentary canal to their final position."

17. Summary: The description of the development of all embryonic structures related closely to the anomaly under discussion has been carried forward to the completion of the process or to a developmental stage beyond which there could be no further possible relation with this specific anomaly either in the positive sense of being a factor directly productive of error or in the negative sense of limiting the error to the factor suspected of producing it.

CORRELATION OF EMBRYOLOGIC FACTS WITH ANATOMIC AND CLINICAL FINDINGS

[NOTE.—It is assumed here that structures and organs which were not found abnormal at operation and which did not at the time of birth or during the successive eleven years show themselves to be abnormal either anatomically or functionally are, in all probability, normal.]

The following structures and organs, closely related embryologically, were normal at birth and during the following eleven years:

1. Umbilicus and attachment of the umbilical cord.

2. Penis and penile portion of the urethra (pars cavernosa) to the point of junction of the urethrorectal fistula.

3. Testes and scrotum.

4. Bladder, membranous portion of the urethra, prostatic portion of the urethra, ureters and pelves of the kidneys.

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45. Keith,[10] p. 303. Bailey and Miller,[16] p. 347.

46. Arey,[39] p. 125.

47. Keith,[10] p. 326.

5. Sphincter urethrae membranaceae and vesical musculature, including vesical sphincter (annulus urethralis).

The following structures were abnormal:

1. Anus.
2. Sphincter ani externus.
3. Lower part of the rectum.
4. Sphincter ani internus.
5. Fistula or tract between the rectum and the urethra.

From these facts, in view of the embryologic study, one may with reasonable certainty assume:

1. The allantois went to its normal termination as the middle umbilical ligament. (See section on embryology, paragraphs 4, 6 and 13, and figs. 3, 4, 5, 6, 7, 8, 9, 14, 15 and 17.)

2. Normal development took place in the fusion of the cloacal tubercles into one and the subsequent development of the penis was normal. Also, the pars pelvina and pars phallica of the urogenital sinus and urethral plate went on to the normal development of the prostatic, membranous and cavernous (penile) portions of the urethra up to the point of the beginning of the tract between the penile portion of the urethra and the rectum. (See section on embryology, paragraphs 10, 11 and 12, and figs. 1, 2, 11, 13, 16 and 17.)

3. The testes apparently developed normally and descended normally into a scrotum which developed normally from the genital folds or the unpaired scrotal area. (See section on embryology, paragraphs 7 and 12, and figs. 1, 2, 13 C, 13 D and 17. In these illustrations the testes have been omitted to prevent confusion.)

4. The bladder anlage portion of the urogenital sinus went forward to the development of a normal bladder. Likewise, the ureteral or kidney buds formed normal ureters and renal pelves. The fact that the lower part of the bladder was apparently normal leads one to believe that the wolffian ducts, from the lower ends of which the mesodermal portion of the bladder is formed,[48] developed normally. (See section on embryology, paragraphs 5, 7, 10 and 13, and figs. 1, 2, 5, 6, 7, 8, 9, 11, 16 and 17.)

5. The normal emptying and the normal sphincteric action and control of the bladder at birth and for eleven years afterward indicate that the original sphincter cloacae developed normally to form the sphincter urethrae membranaceae and that the musculature of the bladder with the formation of the annulus urethralis (vesical sphincter) took place in the normal manner. (See section on embryology, paragraph 14, and fig. 12.)

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48. Keibel and Mall,[11] p. 878.

6. The anus was completely absent at birth. One of two conditions may have been present during embryologic growth:

(*a*) The proctodeum, or anal pit, of the ectodermal cloaca may never have formed.

(*b*) It may have formed, but owing to the abnormal behavior of the entodermal cloaca and urorectal fold, as will be shown in a later paragraph, no entodermal anal membrane was present, and the existing anal pit of the ectoderm may have been filled out by connective tissue from above and thus obliterated. Keibel and Mall [49] commented on this connective tissue infiltration. The fact that every other part of the ectodermal cloaca (the phallus, genital folds and urogenital sinus membrane) developed normally leads me to believe that at some time the anal pit had been present. (See section on embryology, paragraphs 5, 8, 9, 10, 11, 12 and 14, and figs. 1, 2, 5, 6, 7, 8, 9, 11, 13, 14, 15, 16 and 17.)

7. At birth, as has been stated, there was no indication of an anus, nor did I see or feel the elevations caused by the presence of an external sphincter ani as described in paragraph 14 of the section on embryology and mentioned by Young [50] in a case in which a dimple was present at the anal site and the sphincter could be felt and made to contract with a pin prick. It is possible that had I palpated the anal area more carefully or been informed of the pin prick test I might have determined the presence of the sphincter. That a sphincter was present is without question, as was demonstrated by the functionally good anus which resulted after operation. The presence of a sphincter ani further establishes the fact that the cloacal sphincter developed normally. That others, like myself, have been unable to find any trace of an anus is corroborated by at least one excellent observer.[51] (See section on embryology, paragraphs 9, 10, 11 and 14, and figs. 1, 2, 12, 13, 16 and 17.)

8. The presence of the rectal pouch, as found at operation, in the curve of the sacrum and close to the sacrum indicated that some fixation of the posterior rectal mesentery had taken place. (See section on embryology paragraph 16, and figs. 1, 2, 16 and 17.)

9. Regarding the internal sphincter ani, it can be definitely stated that at operation no caudal thickening or swelling of the rectum was seen or felt. The part of the rectum at which this swelling should normally be present was involved in the main part of the anomaly, to be described in the next paragraph. One cannot definitely state that the internal sphincter was absent, but one can state that it was not normal

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49. Keibel and Mall,[11] p. 325.

50. Young,[2] pp. 556-557.

51. Wakeley, C. P. C.: J. Anat. **57**:216, 1923.

in size or location. (See section on embryology, paragraph 15, and figs. 11 and 15 *A*).

10. The presence of the tract or fistula between the rectal pouch and the posterior part of the penile portion of the urethra in this case was apparently due to two factors:

(*a*) The determining factor of the entire anomaly, which was the abnormal behavior of the urorectal fold in not completing its descent to the cloacal membrane. This resulted in two definite errors: The first was a persistent opening between the rectum and the pars phallica of the urogenital sinus, the opening having the diameter of the rectum; in other words, there was a persistent cloacal duct, as shown in figure 15 *B*. The second error was a failure of localization of an entodermal anal membrane.

(*b*) The modifying factors, which converted the large persistent cloacal duct into a comparatively narrow tract of some length, as found at operation, between the rectal pouch and the penile portion of the urethra. I believe that a very small part of this tract consisted of a part of the posterior or proximal part of the penile portion of the urethra, and the major part, of the terminal portion of the rectum, including that part of the rectum which normally should form the internal sphincter, and that the factors producing this result were the gradual pulling back of the rectum into the sacral curve, as found at operation, by a continued effort at fixation of the lower part of the rectum by its mesentery, and by the downgrowth of mesodermal connective tissue around the tract, this connective tissue normally forming the perineum and causing a normal posterior displacement of the lower part of the rectum and of the anus. The normal pushing forward of the pars phallica by the pars pelvina of the urogenital sinus may also have been contributory in converting the opening into a tract. The fact that the lower part of the rectum was at least 1½ to 2 inches (3.7 to 5 cm.) above the perineal level and the fact that the abnormal tract was also some distance from the perineum make it seem probable that there was also a growth of connective tissue from below, possibly from the mesoderm, which by some authors is said to exist in the cloacal membrane and by others to be pushed to the side of the cloacal membrane. At operation connective tissue was present in the areas just described. In paragraph 6 of this section on correlation the absence of the anus was discussed. In view of what has just been stated, a comparison of figures 16 *A* and 16 *B* discloses that even if a definite proctodeum had formed (as in figure 16 *A*) there would have been no rectum with which it could have united to form a normal anal orifice; this is demonstrated in figure 16 *B*. (See section on embryology, paragraphs 5, 6, 8, 9, 10, 11, 12 and 16, and figs. 1, 2, 6, 7, 8, 9, 14, 15, 16 and 17.)

Time at Which the Anomaly Was Determined.—It must be borne in mind that there is considerable variation in the relation of size to the stage of development of many of the structures mentioned in this article. This is unquestionably due to the fact that variation occurs in different embryos. For example, Keibel and Mall [18] stated that in Keibel and Elze's cases, a cloacal duct was present in 11 and 12.5 mm. embryos, that at 15 mm. the cloaca was not fully divided and that it was divided down to the cloacal membrane only at 15.5 mm.; yet they presented a drawing,[52] a copy of which is shown in figure 15, of a model of an embryo of only 11 mm. in which the cloaca is divided down to the cloacal membrane. Allowing for these minor variations, one may say:

1. At five weeks the cloaca is undivided. (See section on embryology, paragraphs 3 and 5, and fig. 5.)

2. At 6 weeks the cloaca is divided almost to the cloacal membrane, with the formation of a cloacal duct. (See section on embryology, paragraphs 3 and 5, and figs. 6, 9 *B* and 14.)

3. At 7 weeks the cloaca is completely divided down to the cloacal membrane. (See section on embryology, paragraphs 3 and 5, and fig. 15 *A*.)

4. At a little less than 8 to 9 weeks the primitive perineum is evident, and the anal pit is also present. (See section on embryology, paragraphs 3 and 10, and figs. 11, 13 *B* and 16 *A*.)

5. From the eighth to the ninth week the anal membrane breaks through to form the anal canal. (See section on embryology, paragraphs 3 and 11, and fig. 13 *C*.)

6. After the middle of the fourth month mesenteric fixation takes place and is continued until birth. (See section on embryology, paragraph 16.)

7. From these statements one may conclude with reasonable certainty that the anomaly started at about the sixth week and was definitely determined at the seventh week so far as the connections between the rectum and the pars phallica of the urogenital sinus is concerned. At from eight to nine weeks the absence of the anus was determined. The changing of a simple opening between the rectum and the penile portion of the urethra (pars phallica) into a definite tract was a secondary and later development which started at about eight to nine weeks with the laying down of the primitive perineum by mesodermal connective tissue and which was augmented after four and one-half months by the continual effort at fixation of the lower part of the rectum by the posterior mesentery until birth. The pushing forward of the pars phal-

52. Keibel and Mall,[11] p. 874.

lica of the urogenital sinus by the pars pelvina begins with the development of the phallus at eight and a half to nine weeks.

Summary.—Two definite but closely related and dependent anomalies existed: (1) an abnormal lower rectal part which had been stretched out into a tract of small caliber to communicate with the proximal part of the penile portion of the urethra and (2) a complete absence of the anal canal, with an imperforate external sphincter.

The first of these was caused primarily by a persistent cloacal duct which the constant effort at fixation of the lower part of the rectum by its mesentery and invasion by connective tissue converted into a tract, largely at the expense of the terminal portion of the rectum and its internal sphincter. The second in all probability was dependent on the first. The anal pit was probably present at some time, but owing to the misbehavior of the entodermal cloaca no connection of the ectodermal and of the entodermal membrane and anal pit with the terminal portion of the rectum could be established; hence, the anal pit was completely obliterated and smoothed out by connective tissue. This, in view of the facts presented, seems far more likely than that no anal pit was formed.

The anomaly was caused entirely by the factors just stated. The embryonic development of all other structures intimately related had no direct or contributory influence on the development of the anomaly.

The anomaly was determined at about the sixth week of embryonic life and was modified throughout the remainder of intrauterine life until it reached the development present at the time of birth.

SUMMARY AND CONCLUSIONS

A rare anomaly is presented. The patient, a boy, was operated on at 48 hours of age by primary perineal plastic operation. An attempt was made to establish an anus and to close the fistula between the urethra and the rectum.

The result of the operation was a very good anus with effective, if not absolutely perfect, sphincteric control for the period of eleven years during which the patient was under observation. The eradication of the connection between the rectum and the urethra was accomplished, but a fistula between the urethra and the perineal-anal junction, which leaked urine in small amounts during urination only, remained. The major portion of the urine was simultaneously passed in a normal manner through the penile urethra.

Operation for the remaining urethroperineal fistula was postponed until the boy should be older, in better health and more manageable.

The embryologic development of this anomaly can, in my opinion, be clearly explained, as can the approximate time of its determination.

I admit that in attempting to explain an anomaly of this type a certain amount of conjecture is bound to enter, but I am convinced that just as normal embryology included in the beginning much conjecture, which was gradually replaced by facts through minute examination of many normal human embryos, just so careful operative or postmortem examination of every available anomaly will eventually, with compilation of the various findings and correlation of these with normal embryology, replace conjecture with well established facts.

Thus convinced, I have undertaken to correlate normal embryology with the anatomy, function and clinical aspects of one specific anomaly, trying always to confine may statements to authentic facts and drawing, I trust, logical conclusions therefrom. If conjecture or faulty deductions have entered the analysis, they may prove a stimulus to others to express their views and bring these fallacies to light.

ETHYL ALCOHOL AS A GERMICIDE

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Alcohol is probably the most popular of all cutaneous disinfectants. It is generally used in every country, not only in dressing wounds and in preoperative preparation of the surgeon's hands and the field of operation, but for a multitude of minor procedures, such as vaccinations, hypodermic injections and punctures of the skin for blood counts. Reasons for its popularity are obvious: It is relatively cheap and easy to obtain, it is pleasant to use and it "wets" the skin efficiently. An alcohol-soaked pledget can wipe away a certain amount of grease and dirt, and in universal experience its application seems capable of preventing infections from needle punctures and the like.

Laboratory tests, however, as reported in the literature, have on the whole shown alcohol to be but weakly bactericidal, and the prevailing conclusion of present day writers is that whatever efficiency it may have as a cutaneous disinfectant is due mainly to detergent properties.

A study of disinfectants, carried on over a period of several years, has led me to a different point of view. Using original quantitative tests of bactericidal activity, I have found ethyl alcohol, within certain narrow limits of concentration, to be strongly germicidal, both in vitro and on the skin. In addition, certain principles have been discovered which, I believe, govern the proper preparation and effective use of alcohol in surgical procedures.

HISTORICAL REVIEW

Alcohol in wine or in other impure forms has been used for local application in surgical practice since time immemorial. The present connotation of the term, however, is modern.

Lowitz[1] (1796) was the first to prepare alcohol containing less than 5 per cent of water.

Koch[2] (1881) in his monumental study of disinfectants found dilute alcohol a relatively weak bactericide and absolute alcohol as indifferent "as sterile water" against anthrax spores.

1. Lowitz, in Thorpe, T. E.: A Dictionary of Applied Chemistry, London, Longmans, Green & Co., 1898-1900.

2. Koch, R.: Zur Untersuchung von pathogenen Organismen, Mitth. a. d. k. Gsndhtsamte **1**:1, 1881.

It is significant that the comprehensive report of the committee on disinfectants of the American Public Health Association [3] (1888) made no mention of alcohol. Furthermore, in this period of intensive study of bacteria and bactericides, many investigators, including Koch, used alcohol to wash bacteria free from the disinfectant under investigation, unconsciously attributing to the disinfectant any contributory bacterio-toxic or bactericidal action of the alcohol.

Fürbringer [4] (1888) recommended alcohol as an accessory in pre-operative preparation of the hands, to remove fatty material from the skin and permit better contact between the cutaneous bacteria and the germicide to follow. He suggested a procedure (washing in water with brush and soap for one or more minutes, in 80 per cent [or stronger] alcohol for one minute and in 3 per cent phenol or 1:500 or 1:1,000 mercury bichloride solution for one minute) which he claimed was able as a rule to "sterilize" the hands. Modifications of this simple routine have outlasted all other methods of disinfection of the hands.

Reinicke [5] (1894) suggested that alcohol might have some disinfectant as well as cleansing action on the skin and advocated washing for three to five minutes in 90 per cent solution.

Krönig [6] (1894), unable to kill Staphylococcus aureus in vitro with 95 per cent alcohol, suggested that the apparent effectiveness of alcohol in surgical procedures might be due to dehydrating and astringent action, the bacteria being held in the shrunken skin.

Ahfeld [7] (1896) concluded that it is necessary for micro-organisms to be wet for alcohol to be most effective and that skin and mucous membranes are disinfected by a "diffusion-stream" of water and alcohol.

Epstein [8] (1897), in the most carefully conducted experiments up to that time, using various sorts of organisms dried on bits of silk thread, found that of the solutions tested (25, 40, 50, 80, 95 and 99 per cent) the most germicidal was the 50 per cent solution, which was capable of killing test bacteria in five to ten minutes. It is remarkable how many modern textbooks in discussing the disinfectant action of alcohol refer only to this work of Epstein.

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3. Disinfection and Disinfectants, Report of the Committee on Disinfectants of the American Public Health Association, Concord, N. J., Republican Press Association, 1888.

4. Fürbringer, P.: Untersuchungen und Vorschriften über die Desinfcktion der Hände des Arztes, Wiesbaden, J. F. Bergmann, 1888.

5. Reinicke, E. A.: Bakteriologische Untersuchungen über die Desinfektion der Hände, Centralbl. f. Gynäk. **18**:1189, 1894; Arch. f. Gynäk. **49**:515, 1895.

6. Krönig, E. A.: Versuche über Spiritusdcsinfektion der Hände, Centralbl. f. Gynäk. **18**:3, 1894.

7. Ahfeld, F.: Die Wirkung des Alkohols bei der geburtshülflichen Disinfektion, Deutsche med. Wchnschr. **6**:81, 1896.

8. Epstein, F.: Zur Frage der Alkoholdesinfection. Ztschr. f. Hyg. u. Infectionskr. **24**:1, 1897.

Minervini [9] (1898), Salzwedel and Elsner [10] (1900) and others corroborated Epstein's work in general but found that different bacteria show varying degrees of resistance to alcoholic action.

Harrington [11] (1903) demonstrated convincingly that micro-organisms are more susceptible to alcohol when moist than when dry on threads and garnets. He found 60 to 70 per cent the most effective strength against the common vegetative germs (when dry), killing them in five minutes or less at room temperature.

Beyer [12] (1911), in a careful study that has not received due recognition, pointed out the important difference between concentrations by volume and concentrations by weight and showed the great superiority of a solution of alcohol exactly 70 per cent by weight. He claimed that a 70 per cent solution is thirty times as powerful as a 60 per cent and forty times as powerful as an 80 per cent solution and that solutions less than 50 per cent or over 80 per cent (by weight) are of no practical value in disinfection. Failing in his efforts to use suspensions of bacteria because of the rapid bactericidal action of alcohol, he resorted in his experiments to use of Staph. aureus dried on silk threads (table 3 and chart 3).

Gregersen [13] (1915) and Christiansen [14] (1918) repeated Beyer's work with modifications and with slightly different results. They used Staph. aureus dried on garnets. Both investigators found somewhat wider ranges in strength of alcohol to be effective. Gregersen concluded that 70 per cent (by weight) is the concentration of maximum power; Christiansen, 80 per cent (table 3). Christiansen also pointed out a relation between low surface tension and disinfecting power.

Frey [15] (1912) attempted to explain Beyer's results on biochemical grounds, calling attention to the fact that the action of alcohol on albumins is maximal when its concentration is 70 per cent by weight.

9. Minervini, R.: Ueber die bactericide Wirkung des Alkohols, Ztschr. f. Hyg. u. Infectionskr. 29:117, 1898.

10. Salzwedel and Elsner: Ueber die Werthigkeit des Alkohols als Desinfectionsmittel und zur Theorie seiner Wirkung, Berl. klin. Wchnschr. 37:496, 1900.

11. Harrington, C.: The Germicidal Action of Alcohol, Boston M. & S. J. 148:548, 1903.

12. Beyer, A.: Alkoholdesinfektion, Ztschr. f. Hyg. u. Infektionskr. 70:225, 1911.

13. Gregersen, J. P.: Untersuchungen über die desinfizierende Kraft der desinfizierenden Stoffe im Verhältnis zu ihrer Konzentration, Zentralbl. f. Bakt. (Abt. 1) 77:168, 1916.

14. Christiansen, J.: Zur Theorie und Praxis der Alkoholdesinfektion, Ztschr. f. physiol. Chem. 102:275, 1918.

15. Frey, E.: Warum wirkt gerade 70%iger Alkohol so stark bakterizid? Deutsche med. Wchnschr. 38:1633, 1912.

Bills [16] (1926) in a study of fat solvents reported ethyl alcohol to be immiscible with cod liver oil, linseed oil, olive oil and butter and coconut fats. [This throws doubt on the usual teaching that alcohol acts chiefly as a detergent, dissolving the grease and oils on the skin.]

Gershenfeld [17] (1938) found that 95 per cent alcohol requires seven to nine months to kill spores of Bacillus megatherium and Bacillus subtilis and that 2 per cent alcohol in culture mediums is not even bacteriostatic for these organisms.

The foregoing review indicates a singular lack of agreement among outstanding investigators as regards the germicidal power of alcohol, its most potent concentrations and the nature of its action on skin—a lack of agreement reflected in surgical technic today. It was in the attempt to throw light on these problems that the studies reported here were undertaken.

EFFECT OF ALCOHOL ON BACTERIAL FLORA OF SKIN

A method (Price,[18] 1938) was used whereby the effect of a germicide on the bacterial flora of skin may be determined quantitatively. In each of these experiments the hands and arms were first scrubbed repeatedly with sterile water, the washings being used to determine the size of the flora on which the germicide was to act. The entire cutaneous area was then washed in the alcohol solution, care being taken in most instances to avoid friction of any sort. Exactly at the end of the test period all germicidal action was terminated by plunging the hands and arms into sterile water. Scrubbing was then resumed in a second series of basins in order to ascertain the number of viable organisms remaining on the hands and arms. From these determinations the effect of the alcohol could be deduced with a fair degree of precision. To illustrate more fully how such tests are carried out, details of one of them are given in table 1 and chart 1.

Summary results of several such experiments with different solutions of alcohol are shown in table 2.

It will be seen that the 60 per cent solution has almost the same degerming effect as scrubbing, whereas the solutions approximating 70 per cent (by weight) are considerably more efficacious. In solutions above 70 per cent the germicidal power decreases.

Moreover, a comparison of experiment 1 with experiment 2, and of experiment 4 with experiment 5 suggests that degermation of the

16. Bills, C. E.: Fat Solvents. J. Biol. Chem. **67**:279, 1926.

17. Gershenfeld, L.: The Sterility of Alcohol, Am. J. M. Sc. **195**:358, 1938.

18. Price, P. B.: The Bacteriology of Normal Skin: A New Quantitative Test Applied to a Study of the Bacterial Flora and the Disinfectant Action of Mechanical Cleansing, J. Infect. Dis. **63**:301, 1938.

Basin	Scrubbing Time, Minutes	Total Bacterial Count for Basin	Cumulative Totals Washed Off	Actual Totals, or Number of Organisms Left*
				7,922,090 (a)
1	1	1,640,450	5,222,090	6,281,640
2	1	841,750	3,581,640	5,439,890
3	2	1,211,910	2,739,890	4,227,980
4	1	436,800	1,527,980	3,791,180
5	1	348,840	1,091,180	3,442,340
6	1	403,760	742,340	3,038,580
7	1	338,580	338,580	2,700,000 (b)

At this point hands and arms were washed without friction in 65.5% (by weight) alcohol for exactly 60 seconds. Scrubbing was resumed immediately. The temperature of the alcohol was 25 C.

Basin	Scrubbing Time, Minutes	Total Bacterial Count for Basin	Cumulative Totals Washed Off	Actual Totals, or Number of Organisms Left*
				1,686,910 (c)
8	1	146,260	1,036,910	1,540,650
9	1	143,520	890,580	1,397,130
10	1	143,940	747,130	1,253,190
11	1	159,250	603,190	1,093,940
12	1	113,400	443,940	980,540
13	1	133,980	330,540	846,560
14	1.5	196,560	196,560	650,000 (d)

* Total number of bacteria on the hands and arms (a) at the beginning of the experiment; (b) after eight minutes of scrubbing; (c) after application of the germicide, and (d) after the second period of scrubbing. The numbers b and d are arrived at by mathematical projection of the curves produced (fig. 1).
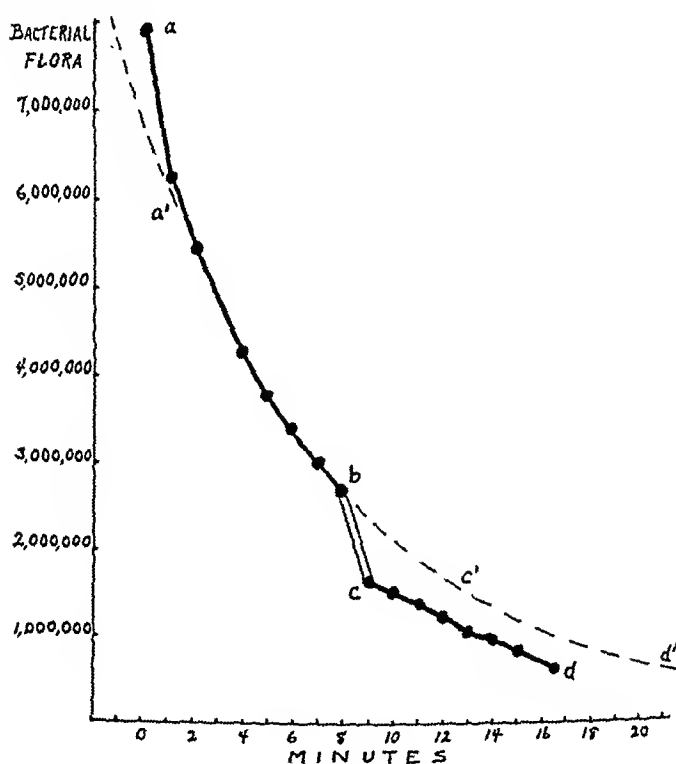
Chart 1.—Effect of 65.5 per cent alcohol on the bacterial flora of the hands and arms. The broken line a'c'd' represents the rate at which the basic flora of my own hands and arms are always degermed by scrubbing in a standard manner. The solid line ab indicates the effect of scrubbing eight minutes, while cd shows the result of scrubbing seven and one-half minutes in the second series of basins. The initial deviation aa' from the standard shows that there were about 1,000,000 contaminating or "foreign" bacteria on the skin, most of which were washed off in the first basin. The second deviation bc was due to use of the alcohol. Note that the same result would have been obtained if instead of washing in alcohol for one minute scrubbing had been prolonged for four and two-tenths minutes, from b to c'. cd is equivalent to c'd'. Hence each minute the hands are kept in this particular solution of alcohol may be said to be equivalent to four and two-tenths minutes of scrubbing.

skin by solutions of alcohol proceeds, as in scrubbing, at regularly logarithmic rates. Further studies have confirmed that observation. Consequently, it is possible accurately to express the effect of the chemical agent in terms of equivalent scrubbing time. Thus, washing for one minute in 69.5 per cent alcohol is equivalent to scrubbing for six and forty-seven hundredths minutes (experiment 5); therefore, washing in that solution for five minutes would have the same result as thirty-two and thirty-five hundredths minutes (5×6.47) of scrubbing. I have found this always to be true, irrespective of the size of the original flora.

In the first 6 experiments (in table 2) particular care was taken to avoid as far as possible any mechanical factor in the action of alcohol on bacteria of the skin. In previous experiments (reported elsewhere)

TABLE 2.—*Effect of Different Strengths of Alcohol on the Bacterial Flora of the Hands and Arms*

Experiment No.	Alcohol Solution Used, Wt. %	Temperature of Alcohol, C.	Length of Time Used, Min.	Friction	Total Organisms Before Use of Alcohol	Total Organisms After Use of Alcohol	Equivalent in Scrubbing Time Actual, Min.	Equivalent in Scrubbing Time Per Min. of Use, Min.
1	59.0	25.5	5	None	1,295,000	660,000	5.33	1.07
2	60.0	24.5	3	None	4,100,000	2,925,000	3.03	1.01
3	65.5	25.0	1	None	2,700,000	1,657,000	4.20	4.20
4	69.0	25.0	3	None	1,400,000	164,000	19.20	6.30
5	69.5	25.0	1	None	2,227,000	1,072,000	6.47	6.47
6	78.5	25.0	1	None	550,000	318,000	4.90	4.90
7	61.0	?	1	Brush	4,350,000	957,000	13.33	13.33
8	70.0	25.0	3	Gauze	1,060,000	29,000	33.74	11.25

it was found that scrubbing with a brush is much more effective in reducing the cutaneous flora than ordinary washing (rubbing the hands together) and many times as efficient as simple rinsing. It seemed probable, therefore, that the action of alcohol would be enhanced by brushing or rubbing the skin. In fact, some heroic surgeons of the past generation advocated and practiced brushing with alcohol, and today many operators are accustomed to rub their hands and arms with gauze soaked in alcohol, but probably more with the idea of cleansing the skin than with any thought of increasing the germicidal effect of alcohol.

Chart 2 shows graphically the result of brushing the skin with 61 per cent alcohol. This relatively inactive concentration was chosen to avoid totals so small, for the second series of basins, as to be hard to plot accurately. A brush ordinarily used for scrubbing was employed. The brushing caused smarting, especially of the arms, sufficiently severe to suggest why the method has never come into general use. Comparison of experiments 2 and 7 shows clearly that brushing has increased enormously the bactericidal effect of alcohol.

Tests have also been made of the effect of rubbing the skin with gauze and 70 per cent (by weight) alcohol. Results of 1 such experiment are shown in table 2 (experiment 8). Before entering the germicide the skin was permitted to dry to avoid any change in concentration of the alcohol by water carried on the hands. Comparison with experiments 4 and 5 indicates that friction in this case almost doubled the bactericidal effect.
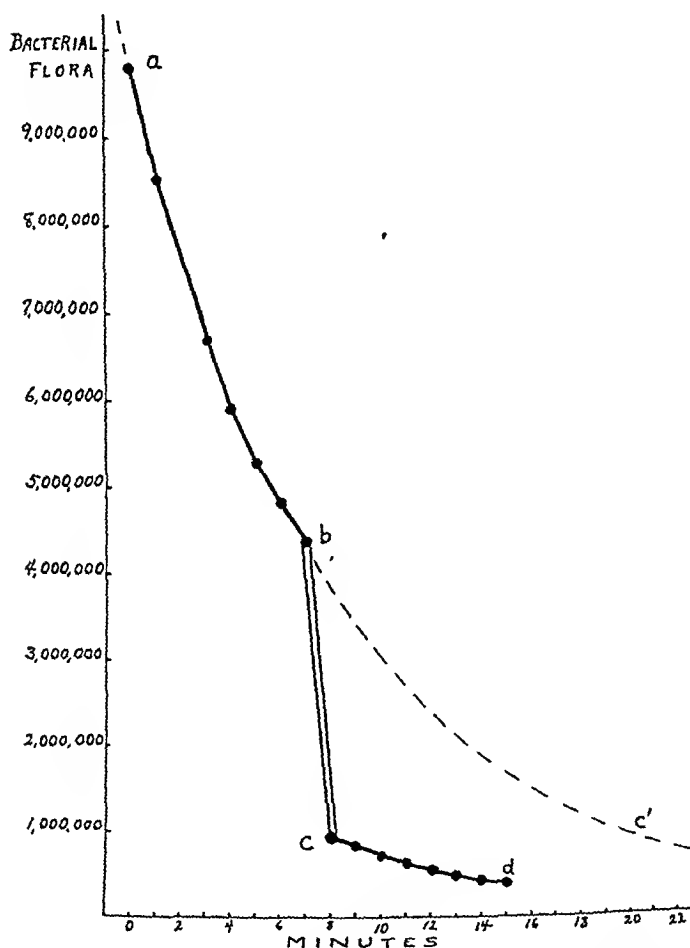
Chart 2.—Effect of 61 per cent alcohol (by weight) used with a brush. *ab,* the result of seven minutes of scrubbing with water; *bc,* the result of brushing the skin with the alcohol; *cd,* scrubbing resumed. *bc* is equivalent to *bc',* or thirteen and one-third minutes of scrubbing.

GERMICIDAL POWER OF ALCOHOL IN VITRO

The experiments reported indicate more surely than any test tube findings what actually happens to the bacterial flora when alcohol is applied to skin. Nevertheless, a better understanding of the mechanism of cutaneous disinfection and the rational use of alcohol in surgical technic requires some definite knowledge of what alcohol does to bacteria in vitro.

Results obtained by Beyer (1911), Gregersen (1916) and Christiansen (1918) are shown in table 3. All three workers used dried Staph. aureus on threads or garnets. All used alcohol by weight per cent, thus avoiding a serious error of earlier, and not a few subsequent,

TABLE 3.—*Time Required by Different Solutions of Alcohol to Kill Staphylococcus Aureus in Vitro (After Christiansen; Adapted)*

Alcohol, Weight, %	Time Required for Sterilization			Alcohol, Weight, %	Time Required for Sterilization		
	Beyer, Minutes	Gregersen, Minutes	Chris-tiansen, Minutes		Beyer, Minutes	Gregersen, Minutes	Chris-tiansen, Minutes
30	..	300	35	70	½	¾	¼
40	>60	37	5	80	22	2	¼
50	47	5	1	90	>60	22	½
60	12	1½	¾	100	..	(>7 days)	>60

Chart 3.—Sterilizing power of solutions of alcohol in vitro. Beyer's results in graphic form.

investigators. All performed their experiments at "room" temperature. Beyer's work is of special interest, and his results when put in graphic form (chart 3) are striking.

It must be kept in mind, however, that all these results are compiled from end point determinations. They leave out of consideration altogether the rate of degermation, a matter of prime importance when applied to cutaneous disinfection. The easy assumption that there exists a close and constant relation between velocity of germicidal action and the time required for complete sterilization is as yet unsupported by experimental evidence.

In a fresh study of this problem use was made of a new quantitative test with bacteria in suspension.

Method.—The test organisms used were Bacillus coli communis, Staph. aureus and Staphylococcus albus, the first two from laboratory stock cultures and the last isolated from my own skin. The organisms were subcultured in infusion bouillon at 37 C. for twenty-four hours. From 1 to 5 cc. of the subculture was added to 100 cc. of sterile distilled water, and this suspension was shaken with beads in a mechanical shaker for twenty minutes or more.

Alcohol: Solutions were prepared with absolute alcohol and distilled water by actual weight.

Technic of Test: Three cubic centimeters of the alcohol solution to be tested was put in a sterile teaspoon, which was held over a beaker containing 197 cc. of sterile distilled water. One capillary drop (0.012 cc.) of the bacterial suspension was added to the alcohol. At the end of the test period, bacteria and alcohol were precipitated into the water below, and the mixture was stirred

TABLE 4.—*Quantitative Study of the Effects of Alcohol on Test Bacteria in Suspension*

Length of Exposure, Seconds	B. coli				Staph. albus			Staph. aureus	
	30% Alcohol	60% Alcohol	70% Alcohol	80% Alcohol	1% Alcohol	50% Alcohol	70% Alcohol	64% Alcohol	70% Alcohol
0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
1	....	....	54.7	....	....	....	15.5	....	3.3
3	....	....	7.0	....	....	....	16.8	32.0	0.3
5	....	....	4.5	....	....	....	8.6	....	....
6	....	....	....	....	....	....	....	36.0	....
9	....	....	....	....	....	....	....	18.0	....
10	....	....	5.8	35.0	....	....	13.0	....	0.7
15	13.6	....	0.6	....	....	....	17.7	....	0.0
18	....	....	....	....	....	....	....	14.0	....
20	11.5	....	1.6	2.0	....	....	7.7	....	....
21	....	....	....	....	....	....	....	11.0	....
25	9.1	....	0.1	....	....	....	0.02	....	0.0
30	9.7	....	....	0.0	....	....	....	....	....
35	....	....	....	....	....	....	0.07	....	....
40	....	4.0	0.0	0.0	....	....	....	....	....
50	....	....	....	0.0	....	....	....	....	....
60	....	0.0	....	0.0	....	0.0	0.0	....	....
90	....	0.0	....	....	....	0.0	0.0	....	....
120	....	0.0	....	....	....	....	0.0	....	....
1200	....	....	....	....	79.0	....	....	....	....

Results are expressed in percentages of surviving organisms. The solutions of alcohol were prepared by the weight-percentage method.

thoroughly with the spoon. The exceedingly rapid diffusion of alcohol in the water is depended on to bring its lethal action to an abrupt termination. Several 1 cc. specimens were taken at once for plating and culture. Controls were observed of the water used, of capillary drops of suspension in 200 cc. of water without alcohol and of capillary drops added after the 3 cc. of alcohol had been put in the 197 cc. of water. (These showed that the alcohol after dilution had no bactericidal or bacteriostatic effect.)

Results.—Results are summarized in table 4. It is admittedly an incomplete study. Several important points regarding the germicidal power of alcohol are brought out by it, nevertheless.

1. Alcohol in proper concentrations is a powerful germicide when in contact with these test organisms in suspension.

2. Alcohol destroys (vegetative) bacteria in aqueous suspension at a constantly diminishing rate. This rate does not appear to be regularly

logarithmic throughout (as in the case with mercury bichloride or phenol) ; there is a sharp immediate reduction, after which the process takes place more slowly.

3. Of the solutions tested, 70 per cent solution (by weight) is the most rapidly bactericidal. Even 1 per cent alcohol, however, kills these test bacteria slowly.

4. Susceptibility to alcohol varies with different kinds of bacteria. The 70 per cent solution appears to be toxic for Staph. aureus in particular. (It is interesting in this connection to recall that Beyer and others used only Staph. aureus as a test organism.)

In the test described, contact between alcohol and bacteria must be almost perfect, surely better than when bacteria are adherent to threads and garnets and far better than when they are concealed deep in crevices and irregularities of the skin. This degree of contact, I believe, explains why the bactericidal power of alcohol is greatest against bacteria in suspension, less when test organisms are attached to threads and garnets, still less when alcohol is rubbed on skin and least of all when alcohol is applied to skin without friction.

ALCOHOL AS A FAT SOLVENT

As has been indicated, alcohol was employed by operators at first solely because of its supposed fat solvent action, and to this day most surgical textbooks recommend its use for that reason. Suspicions as to the accuracy of this view were first aroused when I was unable to recover viable organisms from alcohol in which hands and arms had been washed.

A variety of fats may be encountered on the skin, some of which are collected by contact with greasy or oily objects and others of which are supplied by secretions of the skin itself. The former group is made up chiefly of grease from food and of hydrocarbons which abound in a machine age. Indigenous fats come from the sebaceous glands, which secrete an oily liquid that "sets" on exposure to air. Its exact composition is not known, but it contains fats, soaps, cholesterol, albuminous material, epithelial cells and inorganic salts (Howell,[19] 1924).

To represent this collection of fats I have chosen for the purposes of study: (*a*) petrolatum, a typical hydrocarbon, (*b*) olive oil, almost pure olein, and (*c*) hydrous wool fat, a typical ester of cholesterol. The results of solubility tests are, briefly:

1. Petrolatum is practically insoluble in cold alcohol.

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19. Howell, W. H.: Textbook of Physiology, Philadelphia, W. B. Saunders Company, 1924, p. 883.

2. At room temperature, 1 part of olive oil is found to be completely dissolved in 65 parts of pure alcohol in three minutes, in 325 parts of 95 per cent (by volume) alcohol in eight minutes and in 650 parts of 80 per cent (by weight) alcohol in ten minutes. The amount of olive oil dissolved by 650 parts of 70 per cent (by weight) alcohol after four hours' contact is scarcely detectable.

3. Hydrous wool fat is insoluble in ethyl alcohol.

It seems clear, therefore, that in its strongly germicidal concentrations alcohol is not a fat solvent and that its disinfecting action on skin must be largely or entirely independent of such a property.

PREPARATION AND EFFECTIVE USE OF GERMICIDAL SOLUTIONS OF ALCOHOL

Concentration of alcohol in solutions is by no means simple. Accurate preparation of solutions of alcohol and, conversely, determination of the concentration of alcohol in any given aqueous solution, are complicated by three variables, i. e., specific gravity, temperature expansion, and reaction contraction.

One cubic centimeter of pure distilled water at 4 C. weighs exactly 1 Gm. Since water expands only slightly on heating, this relation between volume and weight remains practically unaltered by variations in temperature, so that quantities of water may be measured by volume or weight interchangeably and fairly accurately. Not so with alcohol. Alcohol is lighter than water; so 1 cc. weighs less than 1 Gm. And because alcohol is very expansile, 1 cc. of warm alcohol weighs less than 1 cc. of cold alcohol. The same is true of any solution of alcohol, to a degree depending on the relative proportion of the ingredients. Preparation of exact concentrations of alcohol by volume is further complicated by the fact that 1 cc. of water plus 1 cc. of alcohol comes to less than 2 cc. of the mixture, for a contraction takes place with production of heat, a contraction which becomes even more pronounced as the solution cools.

Concentration of alcohol may be expressed either as volume per cent or as weight per cent. Volume per cent indicates the number of cubic centimeters of pure alcohol in each 100 cc. of solution. Weight per cent indicates the number of grams of pure alcohol in each 100 Gm. of solution.

Seventy per cent alcohol by volume is commonly prepared as follows: Seven hundred and thirty-seven cubic centimeters of commercial (approximately 95 per cent) alcohol ($\frac{700}{0.95}$) is added to water sufficient to make 1,000 cc. But the weight content of pure alcohol in such a solution is uncertain, owing to variations in the concentration of different lots of

commercial alcohol, to variations in the temperature of alcohol when measured and to the different effects of measuring the water before adding it to the alcohol and of simply adding water up to the 1,000 cc. mark. It is easy to see, therefore, how the bactericidal action of any given solution of alcohol prepared by volume might vary widely from time to time and would be unpredictable even when employed in tests at a standard temperature. Seventy per cent alcohol by weight, on the other hand, prepared by combining 700 Gm. of pure alcohol and 300 Gm. of distilled water, is a uniform preparation having definite and constant bactericidal effect.

Failure of many investigators to appreciate these characteristics of alcoholic solutions or even to recognize the difference between per-
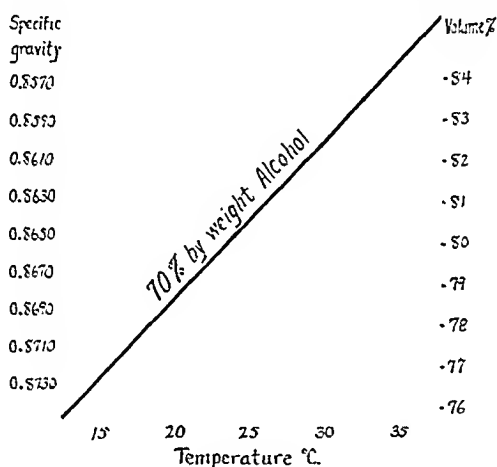
Chart 4.—Chart which may be used with an alcoholometer in preparing 70 per cent alcohol (by weight) from commercial or other solutions of alcohol.

centages by volume and by weight makes it necessary to discount their conclusions as to the germicidal power of alcohol. And because alcohol has so narrow a range of effective bactericidal concentration, surgeons are well advised to keep these points clearly in mind.

In practice it is not feasible actually to weigh out the ingredients of solutions of alcohol. Besides, for the sake of economy one must use commercial instead of pure alcohol. It is possible, though troublesome, to prepare weight per cent solutions from commercial alcohol with the help of a hydrometer, a thermometer and appropriate tables. To be perfectly accurate such solutions should be prepared at the temperature at which they are to be used. To simplify the matter I have prepared and used with great satisfaction a chart (chart 4) which enables one after a little practice to prepare 70 per cent alcohol by weight from

commercial alcohol quite easily. The University Hospital (Tsinan) has for several years employed large, finely graded alcoholometers which have thermometers incorporated within them. One of these is used by the pharmacist in preparation of stock 70 per cent solution; another is kept in the operating room, where a duty of the supervising nurse is to restore used and filtered alcohol to full (70 per cent) strength by the addition of either commercial alcohol or water as may be required.

In operating rooms and physicans' offices, where time or facilities may be lacking for such measurements, 70 per cent by weight can be approximated by taking 810 cc. of commercial (95 per cent) alcohol at operating room temperature (25 C.; 77 F.) and adding cold distilled water to bring the total volume of the solution to 1,000 cc.

Evaporation of alcohol is a matter of practical importance. Pure alcohol is hydroscopic; when exposed to air it gradually approaches 95 per cent. Aqueous solutions of alcohol vaporize by giving off two fractions, 95 per cent alcohol and water. Thus commercial alcohol allowed to evaporate to half its volume will still be 95 per cent. Solutions less than 95 per cent became progressively weaker when exposed because the 95 per cent alcohol content, having a higher vapor pressure than the water fraction, passes off more quickly. Seventy per cent alcohol (by weight) evaporated to half its weight will be found changed to 62 per cent and to have lost most of its germicidal power in the process. This characteristic renders heated alcohol impractical for disinfection of the hands, even though the higher temperature might at first increase the bactericidal activity. And since even slight variations from 70 per cent lessen the disinfectant power of alcohol, it is advantageous to keep solutions covered when not in use.

The quantitative method which has been used in this study may be readily adapted to measure accurately the total bactericidal effect of any routine procedure of preoperative disinfection of the hands. In 1933 I visited eight well known surgical clinics in the United States and abroad, where I was permitted to observe carefully the technic used in operating rooms, both in theory and in practice. From my quantitative studies (those on other germicides than alcohol to be published in the near future) it was estimated that disinfection of the hands as taught and practiced in these clinics resulted in reduction of bacteria to between 50 and 10 per cent of the original flora. That is to say, operators were regularly putting on gown and gloves with as many as 5,000,000, and perhaps not often less than 500,000 organisms, still on their hands and arms.

On the basis of laboratory results, subsequently checked by clinical experience, the following routine is recommended for preoperative preparation of hands and arms. It is a simple method, but it is efficacious in reducing the bacterial flora provided it is followed closely.

1. Scrub the hands and arms thoroughly with a brush, soap and warm water for at least seven minutes. Time taken to trim and clean the nails should not be counted. The effect of such a toilet is to remove practically all ordinary grease and dirt, as well as "foreign" bacteria, and to reduce the "native" skin flora by slightly over 50 per cent.

2. Dry well with a sterile absorbent towel. This step, I have discovered, does not wipe off many bacteria, but it is necessary in order to avoid carrying water into the germicide and changing its concentration.

3. Rinse the hands and arms briefly in 95 per cent alcohol to remove any remaining water. This part of the procedure has relatively little germicidal effect; so there is no advantage in prolonging it. The 95 per cent alcohol carried over into the next basin is helpful rather than otherwise, for it tends to counteract the weakening effect of evaporation on 70 per cent alcohol.

4. Wash the hands and arms in a basin well filled with 70 per cent alcohol (by weight) which has been carefully and freshly prepared. A sterile piece of gauze or a washcloth should be used, and the skin should be rubbed firmly with the germicide. Time is important at this stage. I recommend a full three minutes by the clock. That will reduce the flora, as indicated in table 2 (experiment 8) to about 3 per cent of its former size, or approximately 1.5 per cent of that present before scrubbing was started.

5. Put on gown and gloves. If dry gloves are used, the hands will have to be dried, of course, with a second sterile towel.

The same basinful of 70 per cent alcohol should not be used for too long a period or by too many persons.

Used alcohol, filtered and brought up to correct strength, has been found satisfactory for subsequent use.

The use of 70 per cent (by weight) alcohol is recommended also in preparing the patient's skin for operation. Friction with a gauze sponge increases the germicidal effect. The alcohol should not be followed too quickly by ether, for time is an all-important factor in disinfection.

In another series of experiments, which will be reported separately, alcohol in 70 per cent (by weight) solution was found effective in disinfecting contaminated hands.

SUMMARY

By new quantitative methods, the germicidal power of solutions of ethyl alcohol have been tested, the important difference between concentrations by volume per cent and concentrations by weight per cent being kept in mind.

When used properly, alcohol is an exceedingly efficient germicide, both on skin and against vegetative bacteria in vitro. Exactly 70 per

cent by weight (which has no constant volume per cent equivalent) is the most effective concentration. Even slight variations from this particular strength lessen the bactericidal power of the solution. Seventy per cent by volume is almost useless.

Degermation (a more accurate term than "disinfection") of skin by alcohol takes place at a regularly logarithmic rate. Each minute the skin is kept in 70 per cent (by weight) solution without friction is equivalent to about six and one-half minutes of scrubbing in water. Friction increases the speed of degermation.

This effect is due to inherent bactericidal action and not to any detergent properties, for in its strongly germicidal concentrations alcohol is not a fat solvent.

Against test bacteria in suspension 70 per cent (by weight) alcohol acts even more strongly and rapidly. Higher and lower concentrations are less effective. The rate of degermation of suspensions in vitro does not seem to be regularly logarithmic; there is a large instantaneous drop, followed by more gradual diminution in numbers of surviving organisms.

The difference between the degerming effects of alcohol on skin and in vitro are thought to be due largely, if not entirely, to differences in degree of contact between germicide and bacteria. This explains also why friction increases the germicidal action of alcohol on skin.

Evaporation weakens 70 per cent alcohol and lessens its bactericidal power sufficiently to make this a matter of practical importance.

Difficulties in making accurate solutions of alcohol are discussed, and a relatively simple method of preparing a 70 per cent by weight concentration from commerical alcohol is described.

On the basis of these experimental findings, a routine method of preoperative preparation of the hands has been evolved which, while simple, is a great deal more effective than technics in use at present in many leading hospitals. This procedure has been employed with satisfaction in my operating room for the last four years and, having passed that clinical test, is now recommended to others.

Seventy per cent by weight alcohol is recommended also for use in preparing the field of operation and in disinfecting contaminated hands.

Why exactly 70 per cent should be more toxic for bacteria than any other concentration of alcohol remains an interesting biochemical problem.

PARATHYROIDECTOMY FOR RAYNAUD'S DISEASE AND SCLERODERMA

LATE RESULTS

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In a preliminary report,[1] published in 1935, we described 6 cases of Raynaud's disease and scleroderma treated by parathyroidectomy. At a later date,[2] one of us (J. H. G.) described 2 additional cases. The last report (by J. H. G.), which dealt with the technic of the operation, appeared in the *Journal of the Mount Sinai Hospital* for November 1937. Up to the present writing, the operation has been done in 17 cases. It is our present purpose to appraise the late results in these cases and to state the conclusions which this investigation has led us to form.

It may not be amiss to review briefly certain considerations which led to the rationale of our procedure.

Five years ago we were confronted with a case of generalized scleroderma. The patient was a man who was totally disabled by the disease. We used numerous therapeutic measures without effect, except that the accompanying symptoms of Raynaud's disease in the hands and feet were somewhat improved after calcium therapy. Selye had produced sclerodermatous changes in young rats by the intraperitoneal injection of parathyroid extract. We repeated his experiments on both rats and mice and confirmed his results. As a clinical experiment, therefore, parathyroidectomy was performed on the patient with scleroderma. The result encouraged us to treat other patients in a similar way.

In an effort to understand the mechanism underlying the production of scleroderma by the administration of parathyroid extract we have endeavored to interpret some of the factors in this complex problem.

1. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma: A Preliminary Report, Ann. Surg. **101**:1012 (April) 1935.

2. Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, S. Clin. North America **16**:771 (June) 1936.

Apparently the main function of the parathyroid glands is to control calcium and phosphorus metabolism. This function is accomplished chiefly by mobilization of calcium and phosphorus from the bones. Excessive activity of the parathyroid glands results in decalcification of the bones.

Two forms of hyperparathyroidism are well recognized: (1) that seen in von Recklinghausen's disease, or generalized osteitis fibrosa cystica, in which an adenoma of the parathyroid is commonly found, and (2) the form described by Albright and his co-workers,[3] in which there is diffuse hyperplasia of the glands accompanied by recurring nephrolithiasis. Removal of the adenoma in the first instance and partial parathyroidectomy in the second are effective methods of treatment. A third form of disturbance of parathyroid function has been noted, namely, the hyperplasia frequently associated with rickets and osteomalacia.[4] In these conditions the calcium stores of the body are depleted as a result of deficient intake or absorption, and the parathyroid glands apparently must increase their activity in order to withdraw sufficient calcium from exhausted stores to supply the needs of the blood. This compensatory overactivity may be regarded as a work hypertrophy.

Diets low in calcium are common among adults, and the conditions which govern the absorption of calcium are frequently faulty. Accordingly, various degrees of calcium deficiency may occur, presumably accompanied by corresponding changes in the bones and in the parathyroid glands. It is noteworthy that the total calcium content of the blood is remarkably constant even when the calcium intake is low for a long period. Lennox[5] and his co-workers showed that there was no reduction from the normal calcium content of the blood of subjects starved for twenty-one days. It is therefore obvious that this constancy is maintained by the bones rather than by the diet, which is variable and intermittent. Furthermore, from all the evidence available it seems that the calcium furnished to the blood by the bones is always excreted and is not redeposited in the bones. There is apparently no reversible internal circulation of calcium such as exists, for example, in the case of the bile salts. On the other hand, the calcium absorbed from the intestinal tract is deposited in the bones. The mechanism of this difference in behavior is not clear. That there may be other physiologic

3. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands, Renal Complications of Hyperthyroidism, Am. J. M. Sc. **187**:49 (Jan.) 1934.

4. Cantarow, A.: Calcium Metabolism and Calcium Therapy, Philadelphia, Lea & Febiger, 1933, p. 104.

5. Lennox, W. G.; O'Conner, M., and Bellinger, M.: Chemical Changes in the Blood During Fasting in the Human Subject, Arch. Int. Med. **38**:553 (Nov.) 1926.

differences between absorbed calcium and calcium from the bones is suggested by clinical results. For example, the pain caused by muscle spasm in certain persons taking a diet low in calcium but having normal blood calcium is frequently dramatically relieved when a diet containing an adequate amount of the element is given. No detectable rise in blood calcium occurs.

Calcium exists in at least two forms in the blood: (1) that bound to protein (nondiffusible) and considered physiologically inactive, and (2) the diffusible, physiologically active or so-called "available" calcium. Some investigators are of the opinion that there are three or even four forms of calcium in the blood. It is possible that these different forms may vary in amount without reflecting changes in the total quantity. This phase of calcium metabolism is unexplained. But it is known that if the diffusible calcium is reduced in amount, as it is in the presence of tetany, muscular irritability is increased. This behavior may be considered the reaction of muscle tissue to the fundamental effect of calcium on cell permeability. For normal function, cells are dependent on the presence in their surrounding mediums of certain electrolytes, chiefly calcium, sodium and potassium in balanced proportions. Calcium has a consolidating, stabilizing effect on colloidal systems, so that it may be said to reduce the permeability of cells. On the other hand, sodium and potassium have a liquefying action on cell membranes and may be said to increase their permeability. Bayliss[6] has stated: "We have found reason to look on an increase of permeability of a membrane as an intimate part of the excitatory process, and inhibition, as the opposite process, would thus be associated with decrease of permeability." Thus, when calcium ions are reduced in the blood, cells may manifest increased excitability according to their function; for example, muscle cells would tend to overcontract and become spastic, while nerve cells would show increased irritability.

Obviously, in the reactions of the body to a decrease or lack of essential substances, the constitutional factor plays an important role. The constitutional factor may be considered a local hypersensitivity or inferiority which renders tissues more susceptible to unfavorable environment. As a result of observations covering a number of years, one of us (A. R. B.) formed the opinion that in certain persons a continued calcium deficiency may increase a predisposition to vasospasm. In diseases in which some of the symptoms are due to vasospasm, relief in a large number of cases has followed the use of a diet adequate in calcium.

It is our concept that in cases in which the disease responds to calcium treatment the parathyroid glands are relieved of their extra

6. Bayliss, W. M.: Principles of General Physiology, ed. 3, London, Longmans, Green & Co., 1920, p. 426.

and feet. Parathyroidectomy was performed on June 22. Two and two-thirds parathyroids were removed. Microscopic examination showed scattered areas of hyperplasia.

The immediate postoperative result was excellent. The cutaneous discoloration disappeared. The temperature of the skin showed an elevation of 3 degrees. Within a year, considerable improvement was noted in the scleroderma; the softening involved the fingers, the hands and the face.

Late Follow-Up.—The patient died of an intercurrent infection in 1936.

CASE 4 (previously reported).—M. M., a woman aged 33, was first admitted to the medical service of the Mount Sinai Hospital on Nov. 10, 1933. Symptoms of Raynaud's disease extended over a period of ten years, with involvement of the toes and fingers. For the past two years sclerodermatous changes involving the face, the hands and the fingers had been noted.

Examination showed scleroderma of the face, producing retraction of the lip and inability to close the mouth. The sclerodermatous process involved also the neck, the forearms, the hands and the feet. There was mottled blue discoloration of the toes and fingers. The value for calcium was 10.4 mg., that for phosphorus 4.9 mg. and that for phosphatase 1.9 units per hundred cubic centimeters of serum. Oscillometric determinations showed diminution at the forearms, the wrists, the legs and the fingers. Parathyroidectomy was performed on March 26, 1934. Four parathyroids were isolated, and two glands were removed. Histologically these were found to be normal.

The immediate postoperative response was excellent. The skin was considerably softened. The blueness of the fingers and toes disappeared. At no time was there evidence of tetany.

Late Follow-Up.—Recent examination, four and a half years after the operation, showed that the skin of the face had again become sclerodermatous. The improvement in the hands and feet had not been maintained. Discoloration of the fingers had returned. This result must be classed as a failure.

CASE 5 (previously reported).—R. F., a woman aged 50, was first seen on June 8, 1934, with a three year history of Raynaud's disease involving the hands and feet.

Examination showed rather extensive scleroderma, involving the face, the hands, the feet, the forearms and the legs, with blueness of the fingers and a marked lowering of the surface temperature. Oscillometric determinations showed diminution at the ankles, the feet and the wrists. The cold water test produced the changes typical of Raynaud's disease. The value for calcium was 9.9 mg., that for phosphorus was 3.8 and that for phosphatase was 2.1 units per hundred cubic centimeters of serum. Parathyroidectomy was performed at Mount Sinai Hospital on July 18. Two and two-thirds glands were removed. Histologic examination of the glands showed isolated areas of hyperplasia. Convalescence was uneventful. Immediate improvement in the color of the fingers was noted.

Late Follow-Up.—Four years after the operation the skin of the face, the forearms, the hands and the legs had assumed a normal texture and appearance. It was soft and pliable and did not interfere with motion of the fingers. The patient noticed moderate blueness of the finger tips in cold weather. So far as the scleroderma was concerned, the result was excellent. The improvement in Raynaud's manifestations was fair.

CASE 6 (previously reported).—E. A., a woman aged 34, was seen in June 1934. She complained of pain in the hands and legs, of nine years' duration. She

had always been sensitive to cold weather. During the past five years, symptoms developed which were typical of Raynaud's disease. She also presented symptoms strongly suggesting disease of the coronary arteries.

Examination gave essentially negative results except for diminution in the surface temperature of the hands and feet, blue discoloration of the hands and feet and the typical response seen in patients with Raynaud's disease on immersion of the parts in cold water. Oscillometric examination showed diminution in the thigh, the calf, the ankle, the foot, the arm and the wrist. The value for calcium was 9.5 mg., that for phosphorus was 4.3 mg. and that for phosphatase was 1.7 units per hundred cubic centimeters of serum.

After careful study, the diagnosis of Raynaud's disease with probable spasm of the coronary artery was made.

Parathyroidectomy was performed at the New York Hospital on July 21. Four enlarged parathyroid glands were found. Two were removed in toto, and one was subtotally resected. Histologic examination of the excised glands revealed well defined hyperplasia.

The immediate postoperative response was excellent. The blueness of the fingers and toes disappeared.

Late Follow-Up.—Recent examination, four years after the operation showed that the patient occasionally had blueness of the finger tips in cold weather. She voluntered the information that the operation had resulted in marked improvement as far as the subjective complaints were concerned. She had gained considerable weight and was able to carry out her household duties. From our standpoint, the result in this case should be marked fair.

CASE 7 (previously reported).—M. S., a woman aged 27, was admitted to the Mount Sinai Hospital on May 14, 1935, with a history of Raynaud's disease of one year's duration and of sclerodermatous changes involving the hands and face of two months' duration. She lost 25 pounds (11.3 Kg.) in weight.

Examination showed a masklike expression of the face, caused by the scleroderma. There was involvement of the skin of the fingers and hands, with blue discoloration. There was diminution in surface temperature as compared with the normal. There was considerable diminution in the oscillometric readings at the calf, the ankle, the arm and the forearm. The value for calcium was 10.8 mg. per hundred cubic centimeters of serum; that for phosphorus was 4 mg. The cold water test produced a response characteristic of Raynaud's disease. Capillaroscopic studies of the nail beds showed thin capillary limbs, with spasm and hemorrhage.

Parathyroidectomy was performed on June 2. Four parathyroid glands were isolated. Two were removed in toto and one subtotally. Histologic examination showed no abnormalities. The immediate postoperative response was excellent. Capillaroscopic studies showed marked improvement.

Late Follow-Up.—Recent examination, three years after the operation, showed that the skin of the face, the hands and the fingers had resumed its normal appearance. The patient stated that in cold weather a slight blueness could be noted in the finger tips. The result in this case should be considered excellent.

CASE 8 (previously reported).—A. D., a woman aged 35, was admitted to the Mount Sinai Hospital on Jan. 4, 1936, with a history of Raynaud's disease of three years' duration, associated with pain. During the past six months sclerodermatous changes had been noted in the skin of the face and hands.

Examination showed masklike facies caused by scleroderma of the skin of the face, blueness of the fingers and atrophy of the pulp of the right middle finger, caused by an old infection. Scleroderma of the hands and fingers was marked. The value for calcium was 10.8 mg. and that for phosphorus 3.3 mg. per hundred cubic centimeters of serum. The basal metabolism was normal. Oscillometric determinations were slightly below normal. Dermatherm readings of the skin showed considerable diminution in the surface temperature of the fingers and hands. Immersion of the parts in cold water produced a typical attack of local asphyxia accompanied by severe pain in the fingers. Capillaroscopic studies revealed elongated capillary loops with sluggishness of the blood flow, amounting to complete stasis in some areas.

Parathyroidectomy was performed on January 15. Three parathyroids were isolated, two of them being considerably enlarged. Two glands were removed in toto, and half of the third was excised. Histologic examination showed what was thought to represent hyperplasia.

The immediate postoperative response was excellent. The blueness of the fingers disappeared, and no change occurred after immersion in cold water. There was a marked improvement in the surface temperature readings.

Late Follow-Up.—The patient was seen recently, two years after the operation. The skin of the face had returned to its normal state. The masklike expression had disappeared, and the wrinkles in the skin had returned. Slight change was noted in the finger tips. Otherwise the skin of the hands seemed normal. The patient volunteered the information that slight blueness of the finger tips was noted in cold weather. The result in this case should be classed as excellent for scleroderma and fair for Raynaud's symptoms.

CASE 9.—D. P., a girl aged 19, was admitted to the Mount Sinai Hospital on Sept. 1, 1934, with a history of Raynaud's disease extending over a period of three and a half years. This was followed by thickening of the skin of the hands, the elbows, the forearms, the shoulders and the legs. A cervical ganglionectomy had been performed at the Mayo Clinic one year before, with improvement in the color of the skin on the side on which operation was done but not of the sclerodermatous process.

Examination showed an emaciated girl with generalized scleroderma involving most of the skin of the body, with contractures of the elbows, the shoulders and the hands. There was extensive involvement of the face, with retraction of the lips. Roentgenograms of the skeleton showed generalized osteoporosis. Determinations of the surface temperature showed diminution in the temperature of the fingers, the toes and the knees. The value for calcium was 10.2 mg., that for phosphorus was 4.3 and that for phosphatase was 2.2 units per hundred cubic centimeters of serum.

Parathyroidectomy was performed on October 9. Four parathyroids were isolated, two of which were enlarged to three times the normal size. Three glands were removed. Histologic examination showed focal inflammation in one gland.

During the succeeding few months the patient gained considerable weight, but no change was noted in the sclerodermatous process.

Late Follow-Up.—Recent examination, three and one-half years after the operation showed a marked improvement in the scleroderma. The skin of the face, the neck, the forearms and the hands was definitely softer. The contractures of the elbows and shoulders had disappeared. The patient stated that her condition had been much improved by the operation and that she had been able to resume a great many of her activities.

In the latter part of March 1938 the patient was again admitted to the Mount Sinai Hospital, with severe acute glomerular nephritis, to which disease she succumbed a week after admission.

CASE 10.—J. W., a woman aged 34, was admitted to the Mount Sinai Hospital on Jan. 26, 1937, with a history of Raynaud's disease extending over a period of ten years. Thyroidectomy had been performed for toxic goiter in 1923. The symptoms of Raynaud's disease were worse during cold weather and were also aggravated by numerous psychic disturbances. Scleroderma involving the fingers, the hands and the face had been present for two years.

Examination showed thickening of the skin of the face, the hands and the fingers. The thyroid gland was enlarged by reason of the presence of a number of adenomas in both lobes. The values for calcium and phosphorus were normal. The cold water test revealed a response typical of Raynaud's disease.

Parathyroidectomy was performed on February 5. The operation was made difficult by the presence of multiple adenomas of the thyroid and also by scar tissue from the previous thyroidectomy. In spite of this, four parathyroid bodies were demonstrated. Two of them were slightly enlarged; these were removed in toto, and another was subtotally resected. In addition, a thyroidectomy was performed.

The immediate response was not as dramatic as that seen in previous cases. However, there was a definite improvement in the blue discoloration of the fingers, which was a prominent symptom before operation.

Late Follow-Up.—Recent examination, one year after the operation, showed that the thickening of the skin had practically disappeared, especially in the face. The skin of the fingers and hands was considerably softer. However, the changes in color noted before operation were still present. From the standpoint of the scleroderma the result in this case was excellent. The symptoms of Raynaud's disease, however, were not influenced by the operation.

CASE 11.—E. S., a woman aged 40, was admitted to the Mount Sinai Hospital on Dec. 31, 1935. The history was that of Raynaud's disease of the hands and feet, extending over a period of eight years, with aggravation of the symptoms during cold weather. During the past five years the patient had had recurring infections of the fingers, involving the pulp. For the past three years there had been thickening of the skin of the face, producing a masklike appearance, and thickening of the skin of the fingers and hands. Considerable atrophy of the pulp of most of the fingers was noted. Oscillometric determinations were normal. The temperature of the skin was not affected. The value for calcium was 12.5 mg. and that for phosphorus 4.1 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on Jan. 28, 1936. Two parathyroid glands were demonstrated. They were slightly enlarged. These were removed in toto. Histologic examination showed increase in the eosinophilic cells.

The immediate response after operation was satisfactory. The blueness of the fingers disappeared and was replaced by the normal pink.

Late Follow-Up.—A recent check-up examination, two years after the operation, showed that the scleroderma of the face, the fingers and the hands had been considerably improved. However, color changes involving the fingers were still present, although not to the extent noted before operation. The result in this case from the standpoint of the sclerodermatous process may be classed as good, and from that of Raynaud's symptom as fair.

Case 12.—A. H., a woman aged 26, was admitted to the Mount Sinai Hospital on May 28, 1937. The history of symptoms extended over ten years, during which time she had noted a gradual tightening of the skin of the fingers and hands. The tightness had become progressively worse and had been more marked during the last five years. During cold weather blueness of the fingers was noted. The disease finally involved the face, the neck, the upper part of the chest, the forearms, the hands and the feet.

Examination showed extensive scleroderma in the regions enumerated, with atrophy of the fingers and impairment of function in the finger joints. The lips were retracted so as to expose the upper and lower teeth. All examinations of the blood gave negative results. The value for calcium was 10.6 mg. and that for phosphorus 3.5 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on June 6. Two slightly enlarged glands were removed. Histologic examination revealed nothing of note.

Late Follow-Up.—The result in this case has been unusually good. Ten months after the operation the patient had gained 40 pounds (18 Kg.). The cutaneous thickening had almost completely disappeared. The patient was able to close the mouth, and normal function had returned in the fingers.

Case 13.—H. C., a man aged 38, was admitted to the Mount Sinai Hospital on Oct. 21, 1937, and discharged on November 20. The history of symptoms extended over six months, with thickening and tightening of the skin, starting at the fingers and extending to the arms, the legs, the face and the neck. In a short while the skin of the entire body became involved. This rendered locomotion difficult. The disease was accompanied by severe weakness. There were no changes in color.

Examination showed a chronically ill man with an extensive sclerodermatous process involving the entire body. The skin was tight and glazed, and there was atrophy of the musculature of the legs and forearms. All laboratory examinations gave negative results. The value for calcium was 10.6 mg., that for phosphorus was 2.9 mg. and that for phosphatase was 5 King Armstrong units per hundred cubic centimeters of serum. Oscillometric readings showed slight diminution in the legs. The urine contained no arsenic.

Two and one-half parathyroid glands were removed on November 4. The postoperative convalescence was smooth.

Late Follow-Up.—The patient was seen four months after the operation, at which time only slight improvement was noted.

Case 14.—W. D., a man aged 56, was admitted to the Mount Sinai Hospital on Jan. 18, 1938. The history of symptoms extended over a period of two years, with onset of thickening and tightness of the skin, beginning in the hands and wrists and finally involving the entire body. There was blueness of the finger tips, with pain in cold weather. The patient was compelled to give up his work as a letter carrier.

Physical examination showed an extensive sclerodermatous process involving the hands, the forearms, the face, the neck, the chest and the legs. There was limitation of motion in the finger joints. All laboratory examinations gave negative results. The value for calcium was 9.6 mg. and that for phosphorus 4.3 mg. per hundred cubic centimeters of serum.

Parathyroidectomy was performed on January 24. Four parathyroid bodies were isolated; two appeared to be about three times the normal size. Two glands were removed completely and one subtotally.

Follow-Up.—The patient was last seen two months after operation. At that time a noticeable improvement had taken place. There was distinct softening of the skin of the hands and face. Motion in the finger joints had improved. The final result cannot yet be ascertained.

Case 15.—C. S., a woman aged 36, was admitted to the New York Hospital on Jan. 12, 1935, with Raynaud's disease of eight years' duration. The symptoms were typical of this disease and were more marked during cold weather. They consisted of the usual changes in color, accompanied by pain and involving the hands and feet. A few years before admission the tips of two fingers had become gangrenous.

Physical examination gave completely negative results. There was no evidence of scleroderma. A very thorough work-up revealed nothing of note. Values for calcium and phosphorus were normal. Estimations of the cutaneous temperature showed diminution in the temperature of the fingers and the feet.

Operation was done on January 16. Three slightly enlarged parathyroid glands were found; two were removed completely, and one was subtotally resected. Histologic examination of these glands showed nothing of note.

The immediate response was dramatic. Whereas before operation the cold water test produced definite changes of color in both the hands and the feet, postoperative immersion of the parts in cold water for as long as three quarters of an hour failed to reveal any deviation from the normal.

The improvement noted during the postoperative stay in the hospital continued for two or three months. Then all the symptoms returned.

Late Follow-Up.—The patient was recently examined, three years after the operation, and it was found that all the preoperative symptoms had returned. The result in this case should be classed as a failure.

Case 16.—W. McD., a man aged 39, was admitted to the New York Hospital on May 2, 1935, with a history of scleroderma extending over one and a half years. The process originated in the feet and extended up the legs as far as the groins. The hands and forearms became involved at a later date. For two or three months before the patient's admission to the hospital, he had chronic ulcers on the dorsum of each foot, which refused to heal. The patient presented scleroderma of rather severe degree. An ulcer was present on the dorsum of each foot, measuring about 1 inch (2.5 cm.) in diameter. These were extremely painful. The value for calcium was 11.2 mg., that for phosphorus 4.1 mg. and that for phosphatase 1.4 units per hundred cubic centimeters of serum.

Operation was performed on May 15. Four slightly enlarged parathyroid bodies were demonstrated; two were removed in toto and one subtotally. Histologic examination of the glands showed "slight hyperplasia."

Follow-Up.—The patient improved slowly during the first six months.

Late Follow-Up.—The patient was seen two and a half years after operation, and examination at that time showed that the ulcers on the feet were completely healed. The patient had gained considerable weight, in certain parts of the body the scleroderma had improved considerably, and in others the process seemed to be stationary. The operation apparently had resulted in at least a halt of the disease. The result in this case may be classed as fair.

Case 17.—F. B., a girl aged 16, was admitted to the New York Hospital on June 19, 1935, with a history of scleroderma of three months' duration. For two years preceding her admission she had noted tingling of the fingers and feet, with

coldness and blueness in cold weather. Three months previously she had noted tightening of the skin of the hands, the fingers, the forearms and the feet.

Examination showed a poorly developed and poorly nourished girl, considerably underweight, with scleroderma extending over most of the body but especially severe on the hands, the feet and the neck. The cold water test elicited a positive response. The laboratory examinations gave negative results. Oscillometric readings showed a decrease at the ankles and wrists.

Operation was performed on June 22. Four parathyroid bodies were found. Three were removed in toto. Histologic examination of the glands showed infiltration with polymorphonuclear leukocytes, with the formation of what the pathologist interpreted as microscopic abscesses in two or three places.

Late Follow-Up.—The patient was seen two years after operation. She volunteered the information that cold weather no longer bothered her. There were few, if any, changes in color in the fingers.

Examination showed a softening of the sclerodermatous process. The patient had gained considerable weight and was better able to use her hands. The result in this case was classed as good.

COMMENT

We have examined the records and late results of parathyroidectomy in these 17 cases of Raynaud's disease and scleroderma. We have noted in the cases of Raynaud's disease in which the condition was not associated with sclerodermatous change that improvement followed immediately on the operation but did not continue. In all such cases the symptoms eventually returned. Improvement occurred in all cases of scleroderma and was maintained in all but 1. In a number of cases the greatest improvement in symptoms did not immediately follow the operation, as in the cases of Raynaud's disease, but occurred several months later.

From this experience we must conclude that parathyroidectomy should not be performed as the treatment for uncomplicated Raynaud's disease. In this respect we are reversing the opinion expressed in our original paper, published in 1935. If our original concept is correct, namely, that a like mechanism underlies the development of Raynaud's disease and that of scleroderma, it is difficult to explain this variation in the response of these two conditions to the operative procedure. On the other hand, however, we are of the opinion that improvement may be expected to follow parathyroidectomy in cases of scleroderma if the operation is performed in the early stages of the disease, before articular changes and contractures have developed. For obvious reasons, patients with such changes may not be expected to show any considerable improvement, but from our experience it seems that parathyroidectomy may bring about a halt in the progression of the disease.

There seem to be no contraindications to the operation. In none of the patients did symptoms of tetany develop at any time, nor were there any other postoperative complications. There was no mortality.

Criticism may be made that removal of the parathyroid glands may not have anything to do with the improvement noted and that such improvement may be attributed to the unintentional division of sympathetic nerve fibers during the dissection of the neck in the course of the operation. This explanation may possibly account for some of the immediate effects following the operation, before severed sympathetic fibers have had time to regenerate, and may well explain the short-lived, dramatic response in the cases of Raynaud's disease. However, a relation between the parathyroid glands and scleroderma is indicated in the experimental production of scleroderma through the use of parathyroid extract; so it seems fair to attribute the improvement in these cases to removal of the parathyroid glands.

CONCLUSIONS

From examination of the late results of parathyroidectomy in 17 cases we have concluded that the operation has no place in the therapy of Raynaud's disease. While the immediate results are impressive and often dramatic, the late results do not measure up to the expectations expressed in our original paper. However, in the treatment of scleroderma, whether the·condition is generalized or confined to the hands and face, we are of the opinion that parathyroidectomy offers the patient the probability of recession of the disease in the early stages, and of halting of the process in the late ones. At present, no other method of treatment is known to us which offers this outlook to the patient suffering from scleroderma.

REGIONAL REDISTRIBUTION OF BLOOD IN EXPERIMENTAL SECONDARY SHOCK

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Implied in the concept of physiologic homeostasis (Cannon[1]) is the occurrence of translocations of blood in response to normal and urgent stimuli. Such movements of blood have been investigated in relation to certain regions of the body, particularly the spleen (Barcroft and others[2]) and the lungs (Hochrein and Keller;[3] David and Siedek[4]). The exact redistribution of blood in traumatic or hemorrhagic shock has been the subject of much debate. It is evident that the total mass of blood in any area is dependent on the local vascular tonus. That the tone of the blood vessels is altered by secondary shock is well known, but whether in the direction of vasodilatation or of vasoconstriction is not yet well established. The question is raised: Is the alteration of vascular tonus local or widespread? Accepting the observations of Goltz,[5] who showed that a state of splanchnic vasodilatation could be produced in the frog by repeated blows to the abdomen, Fischer[6] concluded that the phenomena of secondary shock might be explained on this basis. Attractive as the hypothesis was, it received little corroboration, as various clinical workers (Wallace, Drummond

1. Cannon, W. B.: Organization for Physiological Homeosteosis, Physiol. Rev. 9:399, 1929.

2. Barcroft, J.; Harris, H. A.; Orahovats, D., and Weiss, R.: A Contribution to the Physiology of the Spleen, J. Physiol. 60:443, 1925.

3. Hochrein, M., and Keller, C. J.: Beiträge zur Blutzirkulation in kleinen Kreislauf, Arch. f. exper. Path. u. Pharmakol. 164:529 and 552, 1932.

4. David, J., and Siedek, H.: Ueber eine unblutige Bestimmungsmethode des Druckes in der Arteria pulmonalis, Ztschr. f. d. ges. exper. Med. 100:54, 1936.

5. Goltz, F.: Ueber den Tonus der Gefässe und seine Bedeutung für die Blutbewegung, Virchows Arch. f. path. Anat. 29:394, 1864.

6. Fischer, H.: Ueber den Shok, Samml. klin. Vortr., 1870-1875, no. 10 (Chir. no. 5), p. 69.

and Fraser [7]) failed to observe splanchnic vasodilatation in secondary shock. However, it has not as yet been tested experimentally, and proof of its incorrectness is based on circumstantial evidence. It has been suggested that, in contradistinction to this splanchnic "pooling" of blood, stagnation of blood occurs in dilated capillaries of the muscles (Starling [5]) as a result of muscular flaccidity and lack of movement. The fall of blood pressure in shock has been explained also by a loss of blood plasma through the walls of excessively constricted peripheral capillaries (Malcolm; [9] Erlanger and Gasser [10]). Peripheral vasoconstriction has also been observed by Seelig and Lyon,[11] while, more recently, peripheral vasodilation has been observed (Smith [12]). The perfusion rate through isolated vascular beds, e. g., the kidney, the bowel or the hindlimb, has been claimed to be diminished in secondary shock (Morison and Hooker [13]). Again, the phenomena of shock have been attributed to a loss of venous tone caused by failure of the venopressor mechanism (Henderson [14]). It is evident that much uncertainty still exists regarding the state of vascular tonus in shock. In the investigation reported here an effort has been made to determine the redistribution of blood in animals with secondary shock with particular reference to:

(*a*) Influence of trauma, hemorrhage, histamine and epinephrine.

(*b*) Presence or absence of splanchnic vasodilation.

(*c*) General or local alterations of blood vessel tonus.

METHODS

Healthy dogs weighing from 10 to 20 Kg. were used in these experiments. Anesthesia was induced by the intraperitoneal injection of pentobarbital sodium. The question arose as to the method to be used for measurement of the regional distribution of blood. In isolated vascular areas which are accessible, such as the hindlimb, kidney, liver, spleen and bowel, this may be determined by means

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8. Starling, E. H.: Nature et traitement du shock chirurgical, Arch. méd. belges **71**:369, 1918.

9. Malcolm, J. D.: On the Condition of the Blood Vessels During Shock, Lancet **1**:497, 1907.

10. Erlanger, J., and Gasser, H. S.: Circulatory Failure Due to Adrenalin, Am. J. Physiol. **49**:345, 1919.

11. Seelig, M. G., and Lyon, E. P.: Further Experimental Data on the Vasomotor Relations of Shock, Surg., Gynec. & Obst. **11**:146, 1910.

12. Smith, M. I.: The Peripheral Vasomotor Mechanism in Experimental Shock, J. Pharmacol. & Exper. Therap. **34**:239, 1928.

13. Morison, R. A., and Hooker, D. R.: The Vascular Tone and the Distribution of the Blood in Surgical Shock, Am. J. Physiol. **36**:86, 1915.

14. Henderson, Y.: Acapnia and Shock, Am. J. Physiol. **21**:126, 1908.

of the plethysmograph. This procedure, however, is subject to two defects: (1) Quantitative studies are not accurate and (2) unavoidable handling of the region to be studied results in an alteration of the local vascular tone. Observation of the rate of flow of a perfusion fluid through a vascular area is a method which can give information limited to the state of local vascular tone, but it is incapable of yielding even approximate quantitative data regarding variations in the total amount of blood in that area (Morison and Hooker[13]). Observation of the exposed region, e. g., the spleen, by direct vision or roentgen rays is obviously inadequate (Barcroft and others[2]). However, direct observation of the cerebral blood vessels through a cranial "window" has yielded excellent qualitative results (Forbes[15]). All these methods have the defect that they are incapable of application to inaccessible areas, such as the lungs and heart. This disadvantage has been overcome to some extent by use of methods of measuring the variations in the rate of blood flow through vascular regions. Such are thermostromuhr method (Schmid;[16] Rein[17]), the balloon method (David and Siedek[4]) and its modification (Blalock and others[18]).

In order to estimate the redistribution of blood in the head, thoracic, splanchnic and peripheral areas the following method was devised. The head area was arbitrarily fixed as extending from the foramen magnum cephalad. The thoracic region was placed as between the clavicles and the xiphisternum, which was demonstrated by dissection to lie on the same sagittal plane as the domes of the diaphragmatic musculature. The abdominal area was placed as between the xiphisternum and the iliac crests. Finally, the peripheral region was determined as lying caudad to the iliac crests and comprising both hindlimbs. The animal was suspended in a frame, from the cross bar. of which hung a sensitive scale attached to a movable platform. The movements of the scale were recorded by means of a pulley-lever arrangement on a kymograph. The area to be weighed was placed on the platform, the remainder of the animal being adequately supported by wooden blocks. Because of the inertia imposed by the rigid vertebral column, calibration of the moving scale was performed with the animal in situ before and after each experiment. The animals were deprived of food for two days prior to each experiment, and the urinary bladder was emptied by catheter. This simple method possesses several advantages:

(*a*) The animal remains intact.

(*b*) There is no disturbance of the vascular bed of the area to be examined.

(*c*) Quantitative results are obtainable and can be recorded graphically.

The results after calibration of the scale were found to be accurate to within 5 Gm. It was found that the scale usually underestimated rather than overestimated the degree of change in weight. Therefore, the results are based on conservative calculations. Simultaneous readings of the blood pressure were obtained from the left carotid artery. Secondary shock was produced by trauma to the hindlimbs and by repeated hemorrhage.

15. Forbes, H. S.: The Cerebral Circulation: I. Observation and Measurement of the Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

16. Schmid, J.: Die grösse des Blutstroms in der Pfortader, Arch. f. d. ges. Physiol. **125**:527, 1908.

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NORMAL REDISTRIBUTION OF BLOOD

The amount of blood in the head and peripheral areas, as evidenced by alterations in weight, remains remarkably constant under the conditions of these experiments. However, in the splanchnic and thoracic areas there occurs a rhythmic variation in the total quantity of blood (fig. 1). This is represented by a slow biphasic curve which is equivalent to a variation of 10 to 15 cc. of blood and is apparently independent of the peripheral systolic blood pressure and of the cardiac and respiratory rates. It is possible that this phenomenon may depend on variations in the activity of the vagus nerve, but there is no proof of this. Control

Chart 1.—Rhythmic variations in the amount of blood in the thorax (normal animal).

experiments were undertaken to determine what effect, if any, the anesthetic had on the regional redistribution of blood. It was found that pentobarbital sodium produces a centripetal flow of blood which is apparent as an increase of blood in the splanchnic and thoracic regions (fig. 2).

REGIONAL REDISTRIBUTION OF BLOOD AFTER HEMORRHAGE

This phase of the investigation was designed to determine the effect of graded hemorrhage and of hemorrhagic shock on the distribution of blood. The criterion of shock was a systolic blood pressure of 60 mm. of mercury (or less) which showed no spontaneous tendency to rise.

Head Area.—Hemorrhage results in a distinct loss of blood from this region (table 1; fig. 3 *A*). The decrease in weight occurs early, and a maximal loss is soon reached. In these experiments the decrement did not exceed 30 to 50 Gm. After the shock level of blood pressure is reached the loss of weight takes place more slowly and to a lesser extent. In the absence of direct observation of the pial vessels during this period of decrease in the blood pressure it is not possible to state that the loss of blood occurs from the brain. On the contrary, it has been shown (Fog [19]) that, while the pial vessels reveal an initial constriction, this is soon followed by dilatation when a fall of blood pressure is induced by
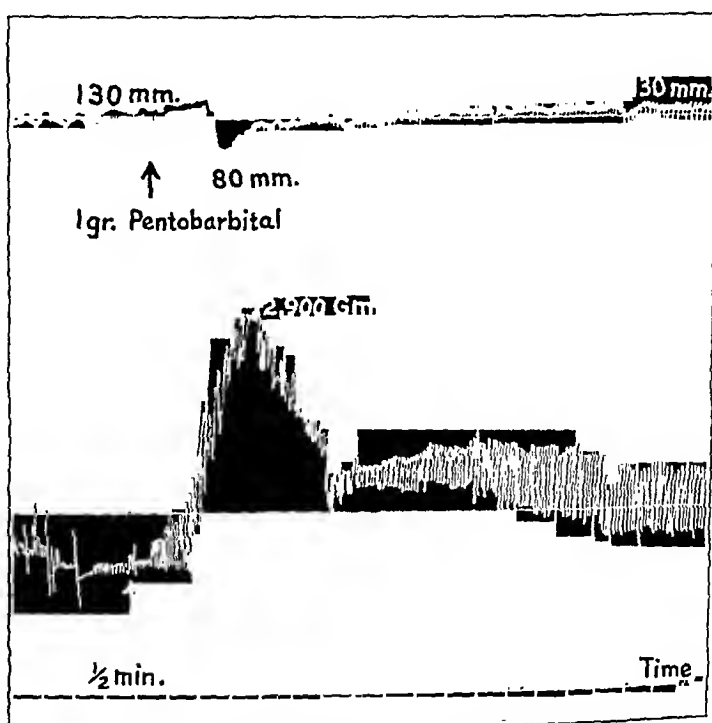
Chart 2.—Influence of pentobarbital sodium on the regional distribution of blood in the splanchnic region.

hemorrhage. The vasodilator impulses to the pial vessels may be mediated through the vagi (Cobb and Finesinger [20]).

Thoracic Area.—In the early stages of hemorrhage a flow of blood takes place into this region, as indicated by a transitory increase in weight (fig. 3 *B*). As the loss of blood continues, a decrease in weight follows which is dependent on the extent of the hemorrhage. The

19. Fog, M.: Cerebral Circulation: The Reaction of the Pial Arteries to a Fall in Blood Pressure, Arch. Neurol. & Psychiat. **37**:351 (Feb.) 1937.

20. Cobb, S., and Finesinger, J. E.: Cerebral Circulation: XIX. The Vagal Pathway of the Vasodilator Impulses, Arch. Neurol. & Psychiat. **28**:1243 (Dec.) 1932.

diminution of blood in this area frequently totals 100 to 200 cc. (table 2; fig. 3 B). The paradoxic shift of blood into the thorax during the early stages of hemorrhage may be explained by an overcompensating splanchnic vasoconstriction and possibly by an increase in the rate and amplitude of the respiratory movements. In these experiments hemor-rhage was continued until shock was definitely present, but at no time was there evidence of vasomotor paralysis in the thoracic area. Active vasoconstriction was observed up to the moment of death (table 2).

TABLE 1.—*Influence of Hemorrhage on the Distribution of Blood in the Head Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Head Area, Gm.	Time, Minutes
8.400	756	...	110	1,550	0
		100	80	1,527	
			90	1,527	
		200	60	1,509	
			30	1,509	
			25	1,509	60
			20	1,509	
			25	1,500	
			25	1,500	80

TABLE 2.—*Influence of Hemorrhage on the Distribution of Blood in the Thoracic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure Mm. Hg	Weight of Thoracic Area, Gm.	Time, Minutes
10,800	972	...	120	4,770	0
		120	110	4,845	
		130	90	4,995	
			90	4,745	
		125	90	4,645	60
			90	4,595	
			85	4,545	
		165	85	4,545	
			30	4,545	
			45	4,520	120

Splanchnic Area.—In this region hemorrhage causes excessive vaso-constriction, so that a large proportion of the blood removed appears to come from the splanchnic area. The loss of weight is greater than can be accounted for by the quantity of blood which has been withdrawn. This would appear to indicate an overcompensating vasoconstriction (table 3; fig. 3 C). That the loss of weight is due to active vasoconstric-tion and not merely to passive removal of blood is indicated by the continued active loss of weight in the splanchnic area in the interval between periods of hemorrhage. Splanchnic vasoconstriction, which is present from the onset of hemorrhage, becomes relatively greater after the shock level of blood pressure is reached and persists until death. In

Chart 3.—*A*, influence of hemorrhage on the regional distribution of blood in the head region. *B*, influence of hemorrhage on the regional distribution of blood in the thoracic region. *C*, influence of hemorrhage on the regional distribution of blood in the splanchnic region.

order to determine to what extent the adrenal glands are a factor in the production of splanchnic vasoconstriction after loss of blood, bilateral adrenalectomies were performed. It will be noted (fig. 3 *C*) that vaso-constriction still occurs in the adrenalectomized animal after hemorrhage. These findings are not consistent with the presence of vasomotor paralysis in the splanchnic area in hemorrhagic shock. However, they do suggest that splanchnic vasoconstriction is dependent not on the presence of the adrenal glands but rather on the integrity of the sympathetic nervous system.

Peripheral Area.—The peripheral redistribution of blood after hemorrhage was studied. In the early stages of hemorrhage, when the blood pressure is still above shock level, a loss of weight takes place from

TABLE 3.—*Influence of Hemorrhage on the Distribution of Blood in the Splanchnic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Splanchnic Area, Gm.	Time, Minutes
8,450	760	...	100	5.535	0
		120	60	5,460	
			55	5,450	
			50	5,435	
			48	5,435	
		115	45	5,435	
			40	5,435	60
			40	5,435	
		60	25	5,260	
			15	5,210	
			10	5,185	
			10	5,160	
			10	5,110	
			8	5,160	
			8	5,085	120

the peripheral region. This suggests the presence of active vasoconstriction which is known to occur in the blood vessels of the skin. This shift of blood amounts to from 20 to 30 cc. If more blood is withdrawn and the blood pressure is brought to the shock level (60 mm. of mercury), the peripheral area regains its initial weight. If additional blood is removed and the blood pressure is lowered to the critical level (20 mm. of mercury), a gradual increase of weight occurs in the peripheral region, which amounts to the equivalent of 25 to 30 cc. of blood (table 4). The later translocation of blood into the periphery may be due to one or more of the following factors:

1. Peripheral vasomotor paralysis (Smith[12]).
2. Excessive peripheral vasoconstriction with a loss of plasma through the capillary walls (Malcolm[9]).
3. Vasoconstriction of the cutaneous blood vessels and vasodilatation of the blood vessels of the muscles (Starling[8]).

The work of various investigators (Seelig and Lyon [11]) indicates that peripheral vasoconstriction rather than peripheral vasomotor paralysis occurs in shock. In support of this it has been shown that the vasomotor reflexes can be elicited even in the presence of advanced secondary shock (Porter and Quimby; [21] Porter, Marks and Swift [22]). Evidence will be presented later in this paper to support the view that the late increase of weight in the periphery results from dilatation of the muscle capillaries and that it corresponds to the type of vascular redistribution produced by the administration of small amounts of epinephrine.

Résumé.—The regional redistribution of blood in the presence of hemorrhagic shock may be briefly recapitulated at this time. A shift of blood away from the head region always occurs. In the thoracic area there is an early increase in weight, probably as a result of excessive

TABLE 4.—*Influence of Hemorrhage on the Distribution of Blood in the Peripheral Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Blood Withdrawn, Cc.	Blood Pressure, Mm. Hg	Weight of Peripheral Area, Gm.	Time, Minutes
7,600	684	..	105	2,760	0
		50	100	2,754	
		50	100	2,747	
		70	60	2,740	
			80	2,773	
			50	2,760	
			55	2,773	60
			60	2,773	
		30	50	2,773	
		30	45	2,780	
			55	2,780	
			45	2,780	
			25	2,786	120

splanchnic vasoconstriction forcing blood into the thorax. Later the weight of the thoracic area decreases. The splanchnic area always shows a decrease in weight, and a large proportion of the blood lost by hemorrhage comes from this region. In a number of the animals in the present series of experiments the splanchnic vasoconstriction was excessive, so that the loss of weight which occurred in the splanchnic region was almost as great as the amount of blood lost by hemorrhage (table 3). Such animals, which may be termed hyperreactors, usually experienced shock more rapidly than did those animals in which excessive splanchnic vasoconstriction was not present. The peripheral region revealed an early loss of weight and then a gradual return to the initial weight level.

21. Porter, W. T., and Quimby, W. C.: Further Data Regarding the Condition of the Vasomotor Neurons in "Shock," Am. J. Physiol. **20**:500, 1908.
22. Porter, W. T.; Marks, H. K., and Swift, J. B.: The Relation of Afferent Impulses to Fatigue of the Vasomotor Centre, Am. J. Physiol. **20**:444, 1904.

In the later stages of hemorrhagic shock an increase of weight occurred, indicating a peripheral "pooling" of blood or blood plasma. The data presented suggest that peripheral vasoconstriction reaches its maximum in an early stage of shock, in contradistinction to splanchnic vasoconstriction, which is progressive up to the time of death.

A comparison was made of the regional changes in weight following hemorrhage. Representative data are shown in table 5, and it will be noted that the lowest percentage loss of weight was obtained in the peripheral area, where a loss of only 0.72 per cent is recorded. The percentage weight loss from the head area was low, being only 3.2 per cent. The dilatation of the cerebral blood vessels (Fog [19]) during hemorrhage was a factor in maintaining blood flow to the brain under the adverse conditions of hemorrhage. The greatest percentage losses of weight took place from the thoracic region and particularly from the splanchnic region, where as much as an 8.1 per cent loss of weight occurred.

TABLE 5.—*Relative Regional Change in Weight Following Hemorrhage*

Region	Weight, Gm.	Weight Loss, Gm.	Weight Loss in Percentage of Regional Weight
Head	1,550	50	3.2
Thorax	4,770	250	5.2
Splanchnic	5,535	450	8.1
Periphery (hindlimbs)	2,760	20	0.72

REGIONAL REDISTRIBUTION OF BLOOD AFTER TRAUMA

In this phase of the study the distribution of blood after trauma was investigated and compared with that after hemorrhage. Traumatic shock was produced by repeated blows to one or both hindlimbs with a padded hammer. Measurements of the regional weight were made prior to the trauma and also during the period of falling of the blood pressure. Care was taken not to break the continuity of the cutaneous surface.

The shift of weight in all areas was somewhat slower than that resulting from hemorrhagic shock. The head region showed a gradual loss of weight which did not exceed 30 to 50 Gm. In the early stages of traumatic shock there occurred an increase of weight in the thorax, but as shock deepened a gradual loss of weight took place (table 6). The total weight loss in all areas examined is obviously dependent on the size and weight of the individual animal. In the splanchnic region there is a progressive loss of weight which continues until death. It is rapid in the earlier phases of shock but becomes slower after the blood pres-

sure has fallen below the shock level. In many of these experiments a loss of weight equivalent to 30 to 40 per cent of the calculated blood volume was present (table 7). These findings suggest that a large proportion of the blood which escapes into the area of trauma is lost from the splanchnic region. The rate of fluid loss into the traumatized

TABLE 6.—*Influence of Trauma on the Distribution of Blood in the Thoracic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Thoracic Weight, Gm.	Time, Minutes
14,500	1,305	....	125	3,900	0
		Trauma	115	4,020	
		Trauma	109	3,975	30
		Trauma	94	3,910	
		Trauma	90	3,880	
		Trauma	85	3,830	60
		Trauma	83	3,800	
			72	3,800	
			60	3,780	
			55	3,775	
			50	3,760	120
			50	3,770	
			45	3,750	
			30	3,735	
			30	3,735	180
			35	3,720	

TABLE 7.—*Influence of Trauma on the Distribution of Blood in the Splanchnic Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Splanchnic Weight, Gm.	Time, Minutes
13,000	1,170	....	110	5.500	0
		Trauma	100	5,475	
		Trauma	95	5,400	30
		Trauma	80	5,400	
		Trauma	90	5,350	60
		Trauma	70	5,375	
			63	5,350	
			50	5,325	
			45	5,300	
			50	5,275	120
			45	5,250	
			30	5,200	
			30	5,200	
			50	5,150	
			47	5,150	180

limbs was largely dependent on the extent and rapidity with which splanchnic vasoconstriction occurred. An increase in weight of the hind-limbs invariably occurred after trauma (table 8). Are we correct in assuming that this increase in weight, which may amount to the equivalent of 50 per cent of the calculated blood volume, is due to the accumulation of blood and blood plasma in the extravascular spaces of

the traumatized tissues? In view of the work of Lewis [23] on the local release of histamine from the skin, it would seem to be more reasonable to regard the increase in weight as being the result of two factors: (1) extravasation of blood and plasma into the extravascular spaces, and (2) dilatation of blood vessels in the area of trauma, particularly in the muscles, with a resulting segregation of blood within these vessels. A third factor, also, may be the imbibition of fluid by traumatized and dying cells. The regional redistribution of blood resulting from trauma was found to be similar to that following hemorrhage.

REGIONAL REDISTRIBUTION OF BLOOD AFTER ADMINISTRATION OF HISTAMINE

An investigation of the distribution of blood after the administration of histamine was undertaken in order to determine whether or not the

TABLE 8.—*Influence of Trauma of the Distribution of Blood in the Peripheral Area*

Weight of Dog, Gm.	Calculated Blood Volume, Cc.	Trauma	Blood Pressure, Mm. Hg	Weight of Hindlimbs, Gm.	Time, Minutes
7,900	711	....	115	2,000	0
		Trauma			
			95		
		Trauma	90		
		Trauma	70		
		Trauma	65		
		Trauma	50	2,320	60
				2,340	
				2,360	
			35	2,400	120
			30	2,435	
			30	2,450	180

activity of histamine-like substances could explain the phenomena of secondary shock. The existence of such toxic substances in secondary shock has been claimed (Cannon and Bayliss;[24] Dale and Richards;[25] Grunke and Haring[26]) and just as vigorously denied (Simonart;[27]

23. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, Ltd., 1927.

24. Cannon, W. B., and Bayliss, W. M.: Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions: VIII. Traumatic Toxaemia as a Factor in Shock, Medical Research Committee, Special Report Series, no. 26, London, His Majesty's Stationery Office, 1919, p. 19.

25. Dale, H. H., and Richards, A. N.: A Vasodilator Action of Histamin and Some Other Substances, J. Physiol. **52**:110, 1918.

26. Grunke, W., and Haring, W.: Das Verhalten der Blutmenge beim experimentellen Shock, Ztschr. f. d. ges. exper. Med. **79**:763, 1931.

27. Simonart, A.: Etude expérimentale sur la toxémie traumatique et la toxémie des grands brulés, Arch. internat. de pharmacodyn. et de thérap. **37**:269, 1930.

Blalock;[28] Roome and Wilson;[29] O'Shaughnessy and Slome;[30] Smith;[12] Schneider;[31] Herbst[32]).

Histamine was injected intravenously in amounts of 0.00005 to 0.0002 mg., and the regional shift of blood was studied. In the head area there occurs a loss of weight with administration of varying quantities of histamine (table 9). It has been pointed out that histamine dilates the cerebral arterioles and causes an increased flow of blood through the brain (Forbes, Wolff and Cobb;[33] Weiss and Lennox[34]). On this basis, the shift of blood observed in the present studies must occur from the skin, muscles or bone of the head region.

In these experiments histamine induced a striking shift of blood into the thoracic region, as was evidenced by the rapid increase of weight. This translocation of blood persisted for long periods (one to three hours) and was present even after the systolic blood pressure had returned to the initial level (table 10; fig. 4 *A*). It was coincident with

TABLE 9.—*Influence of Histamine on the Redistribution of Blood in the Head Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0001 mg. histamine	Blood pressure, mm. Hg	105	45	75	100	.100	100
	Weight of head, Gm......	2,662	—28*	—22	—17	—10	—5
0.0002 mg. histamine	Blood pressure, mm. Hg	115	45	100	110	110	115
	Weight of head, Gm......	2,630	—25	—8	—8	0	0

* Minus sign indicates loss.

the fall in systolic blood pressure. Considerable disagreement exists regarding the effect of histamine on the pulmonary circulation. A fall in

28. Blalock, A.: Experimental Shock: The Probable Cause for the Reduction in Blood Pressure Following Mild Trauma to an Extremity, Arch. Surg. 22:598 (April) 1931.

29. Roome, N. W., and Wilson, H.: Experimental Shock: Effects of Extracts from Traumatized Limbs on Blood Pressure, Arch. Surg. 31:361 (Sept.) 1935.

30. O'Shaughnessy, L., and Slome, D.: Etiology of Traumatic Shock, Brit. J. Surg. 22:589, 1935.

31. Schneider, H.: Ueber das Vorkommen und über die Bedeutung von Gewebsgiften bei Shockzustanden des Menschen, Deutsche Ztschr. f. Chir. 229:343, 1930.

32. Herbst, R.: Experimentelles zur Entstehung des traumatischen Shocks, Arch. f. klin. Chir. 176:98, 1933.

33. Forbes, H. S.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: X. The Action of Histamine, Am. J. Physiol. 89:266, 1929.

34. Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. 26:737 (Oct.) 1931.

pressure in the pulmonary artery has been observed (David and Siedek [4]), while others have found that histamine increases the pulmonary arterial pressure (Hochrein and Keller [3]). It has been demonstrated that histamine, acting mainly on the pulmonary arterioles, constricts both the inflow and the outflow of the lungs (Inchley [35]). This observation has been confirmed by Gaddum and Holtz.[36]

Histamine in small doses produced a temporary shift of blood into the splanchnic region, followed by a decrease in the amount of blood in that area (table 11; fig. 4 B). The increase of splanchnic blood may be explained by temporary constriction of the hepatic veins with retardation of blood flow through the portal vessels (Mautner and Pick; [37] Bauer, Dale, Poulsson and Richards [38]). It is apparent that histamine is much

TABLE 10.—*Influence of Histamine on the Redistribution of Blood in the Thoracic Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0001 mg. histamine	Blood pressure, mm. Hg	110	40	90	110	110	110
	Thoracic weight, Gm.....	5,330	+233*	+200	+166	+100	+100

* Plus sign indcates increase.

TABLE 11.—*Influence of Histamine on the Redistribution of Blood in the Splanchnic Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.0002 mg. histamine	Blood pressure, mm. Hg	100	40	100	100	100	100
	Splanchnic weight, Gm...	2,500	+150*	—50	—50	—25	—25

* Plus sign indicates increase; minus sign, loss.

more effective in altering the thoracic redistribution of blood than the splanchnic. These findings explain the observation that total splanchnic evisceration does not prevent the fall in blood pressure produced by histamine (Gotsev; Lueken and Simmendinger [39]).

35. Inchley, O.: Histamine Shock, J. Physiol. **61**:282, 1926.

36. Gaddum, J. H., and Holtz, P.: The Localization of the Action of Drugs on the Pulmonary Vessels of Dogs and Cats, J. Physiol. **77**:139, 1932.

37. Mautner, H., and Pick, E. P.: Ueber die durch Shockgifte erzeugten Zirkulationsveränderungen, Arch. f. exper. Path. u. Pharmakol. **142**:271, 1929.

38. Bauer, W.; Dale, H. H.; Poulsson, L. T., and Richards, D. W.: The Control of Circulation Through the Liver, J. Physiol. **74**:343, 1932.

39. Gotsev, T.; Lueken, B., and Simmendinger, W.: Ueber den Einfluss des Splanchnicusgebiets auf den allgemeinen Blutdruck, Ztschr. f. d. ges. exper. Med. **100**:81. 1936.

The peripheral distribution of blood is also affected by histamine. With small amounts (0.00005 mg.) there is a loss of blood followed by an increase in weight and finally a return to the initial level (table 12; fig. 5 *A*). With a larger dose (0.0001 to 0.0002 mg.) there is a definite shift of blood into the periphery (table 12; fig. 5 *B*).

It is evident that the redistribution of blood produced by administration of histamine differs from that produced by trauma or by hemor-
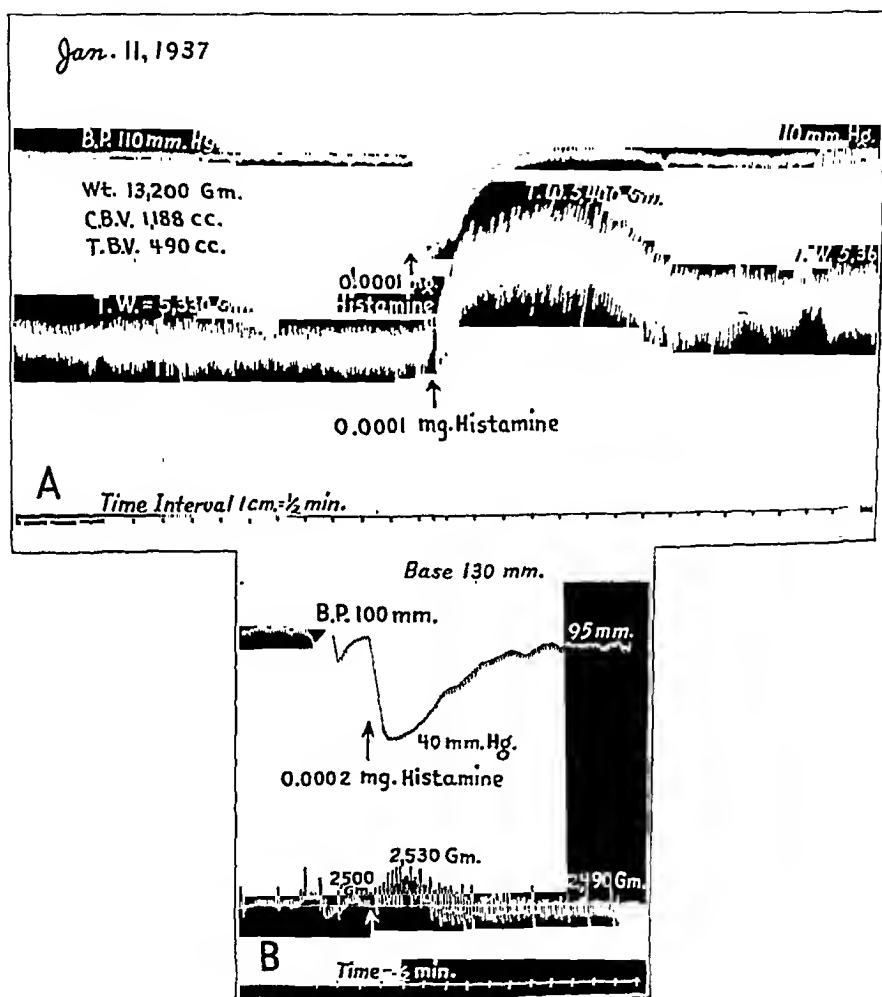
Chart 4.—*A,* influence of histamine (0.0001 mg.) on the regional distribution of blood in the thoracic region. *B,* influence of histamine (0.0002 mg.) on the regional distribution of blood in the splanchnic region.

rhage. Division of the spinal cord does not prevent the fall in blood pressure following administration of histamine. This indicates that the site of action is in the blood vessels (Hermann and Morin [40]).

40. Hermann, H. H., and Morin, G.: Démonstration cruciale chez le chien de l'origine périphérique du collapsus vasculaire dans différents états de choc, J. de physiol. et de path. gén. **33**:833, 1935.

REGIONAL REDISTRIBUTION OF BLOOD AFTER ADMINISTRATION
OF EPINEPHRINE

Following the observation that the administration of large quantities of epinephrine results in a condition of shock accompanied by low blood pressure, diminished blood volume and concentration of the red blood cells, it was suggested that hyperactivity of the adrenal glands might be an etiologic factor in secondary shock (Bainbridge and Trevan;[41] Erlanger and Gasser[10]). Recently, considerable emphasis has been placed upon excessive activity of the adrenal glands as a factor in shock (Freeman[42]). For this reason a study has been made of the redistribution of blood after the administration of epinephrine. Epinephrine hydrochloride was injected intravenously in varying amounts from 0.02 to 3 mg.

After the injection of epinephrine there occurred a distinct shift of blood from the head region, as is shown by the rapid loss of weight

TABLE 12.—*Influence of Histamine on the Redistribution of Blood in the Peripheral Area*

Injection		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.00005 mg.	Blood pressure, mm. Hg.	115	40	105	115	115	115
histamine	Peripheral weight, Gm...	3,570	—50*	—25	0	0	0
0.0001 mg.	Blood pressure, mm. Hg.	95	25	75	75	95	95
histamine	Peripheral weight, Gm...	3,570	+50*	+30	+10	0	0

* Minus sign indicates loss and plus sign increase.

(table 13; fig. 6*A*). This was present both with small and with large doses. That the brain itself may partake of this shift of blood is possible, in view of definite proof of the existence of a vasomotor innervation of the cerebral vessels (Forbes et al;[33] Westenrijk[43]). Moreover, epinephrine has been shown to exert a constricting effect on the blood vessels of the isolated canine brain (Wiggers[44]).

41. Bainbridge, F. A., and Trevan, J.: Surgical Shock and Some Allied Conditions, Brit. M. J. **1**:381, 1917.

42. Freeman, N. E.: Decrease in Blood Volume After Prolonged Hyperactivity of the Sympathetic Nervous System, Am. J. Physiol. **103**:185, 1933.

43. Westenrijk, N.: Untersuchungen über die Wechselbeziehungen der einzelnen Kreislaufgebiete: II. Ueber das vasomotorische Verhalten der Gehirngefässe, Ztschr. f. d. ges. exper. Med. **93**:1, 1934.

44. Wiggers, C. J.: Further Observations on the Constricting Action of Adrenaline on the Cerebral Vessels, J. Physiol. **48**:109, 1914.

In a dose of 0.02 mg. epinephrine causes a flow of blood into the thoracic region which, after several minutes, is followed by a return to the initial level and finally by a slight diminution of the blood in this area (table 14). Large amounts (2 to 3 mg.) produce a marked shift
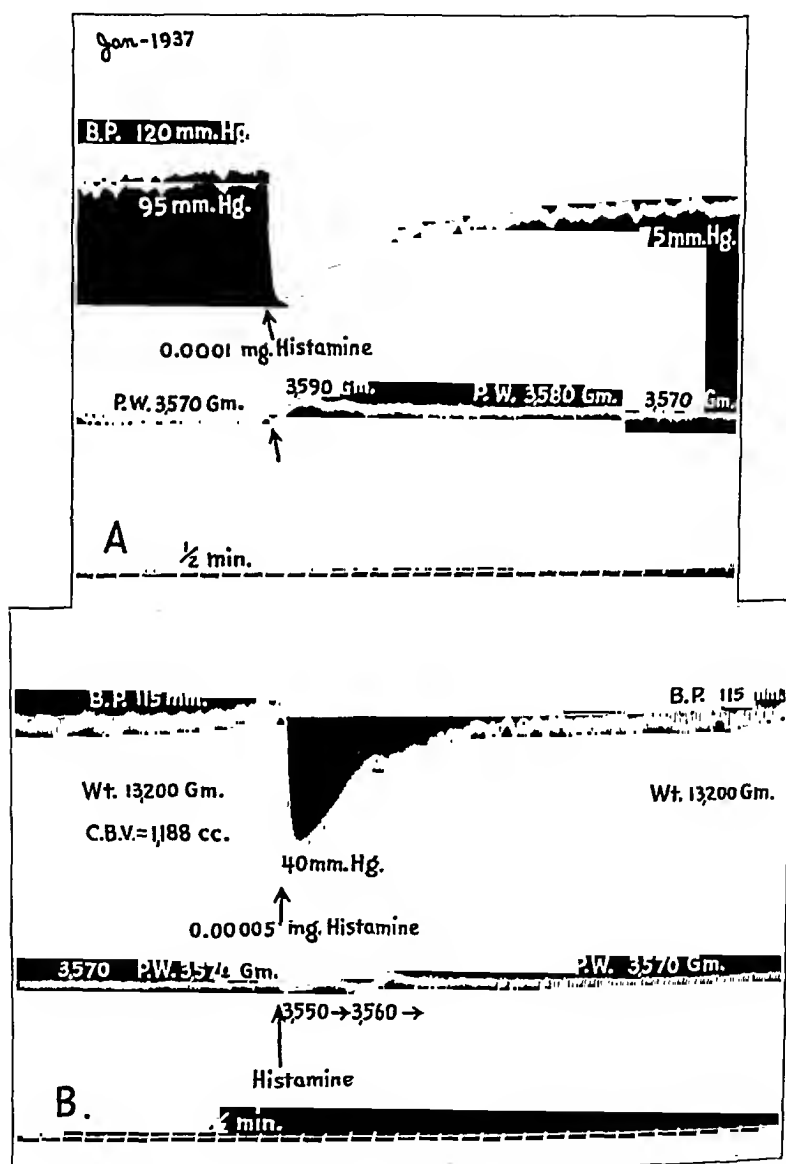
Chart 5.—*A*, influence of histamine (0.0001 mg.) on the regional distribution of blood in the peripheral region. *B*, influence of histamine (0.00005 mg.) on the regional distribution of blood in the peripheral region.

of blood from the thoracic area and a loss of weight which is maintained for periods of one-half to one hour (table 14; fig. 6 *B*). These results are in agreement with those of others, who have found that small amounts of epinephrine cause dilatation of the pulmonary blood vessels,

(Brodie and Dixon; [45] Langlois and Desbouis; [46] Fühner and Starling; [47] Rothlin; [48] Anderes and Cloetta [49]), while large amounts produce pulmonary vasoconstriction (Tribe [50]).

The splanchnic region after the administration of a small amount of epinephrine (0.02 mg.) exhibits a definite and rapid loss of blood (table 15; fig. 7 *A*). This is followed after a variable period by a secondary shift of blood into the splanchnic area, this phase being accom-

TABLE 13.—*Influence of Epinephrine on the Redistribution of Blood in the Head Area*

Experi-ment 27		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	95	120	95	95	100	95
	Weight of head, Gm.....	2,675	—25*	—42	—25	—21	—15
Experiment 25							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	110	180	150	100	70	100
	Weight of head, Gm.....	1,670	—26	—21	—20	—23	—18

* Minus sign indicates loss.

TABLE 14.—*Influence of Epinephrine on the Redistribution of Blood in the Thoracic Area*

Experi-ment 22		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	160	130	130	130	130
	Thoracic weight, Gm....	5,430	+50*	—16	—16	—16	—16
Experiment 23							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	125	240	160	100	100	100
	Thoracic weight, Gm....	5,400	—100*	—130	—166	—200	—233

* Plus sign indicates increase and minus sign loss.

45. Brodie, T. G., and Dixon, W. E.:   On the Innervation of the Pulmonary Blood Vessels and Some Observations on the Action of Suprarenal Extract, J. Physiol. **30**:476, 1904.

46. Langlois, S., and Desbouis, P.:   Adrénaline et circulation pulmonaire, Compt. rend. Soc. de biol. **72**:674, 1912.

47. Fühner, H., and Starling, E. H.:   Experiments on the Pulmonary Circulation, J. Physiol. **47**:286, 1913.

48. Rothlin, E.:   Experimentelle Untersuchungen über die Wirkungsweise einiger chemischer vasotonisierender Substanzen organischer Natur auf überlebende Gefässe, Biochem. Ztschr. **111**:257, 1920.

49. Anderes, E., and Cloetta, M.:   Der Beweis für die Kontraktilität der Lungengefässe und die Beziehung zwischen Lungendurchblutung und O_2- Resorption, Arch. f. exper. Path. u. Pharmakol. **79**:301, 1915.

50. Tribe, E. M.:   Vasomotor Nerves in the Lungs, J. Physiol. **48**:154, 1914.

panied by an increase in weight. With a larger dose of epinephrine (2 to 3 mg.) there occurs an early shift of blood from the region, which is of short duration and is soon followed by a secondary increase in the
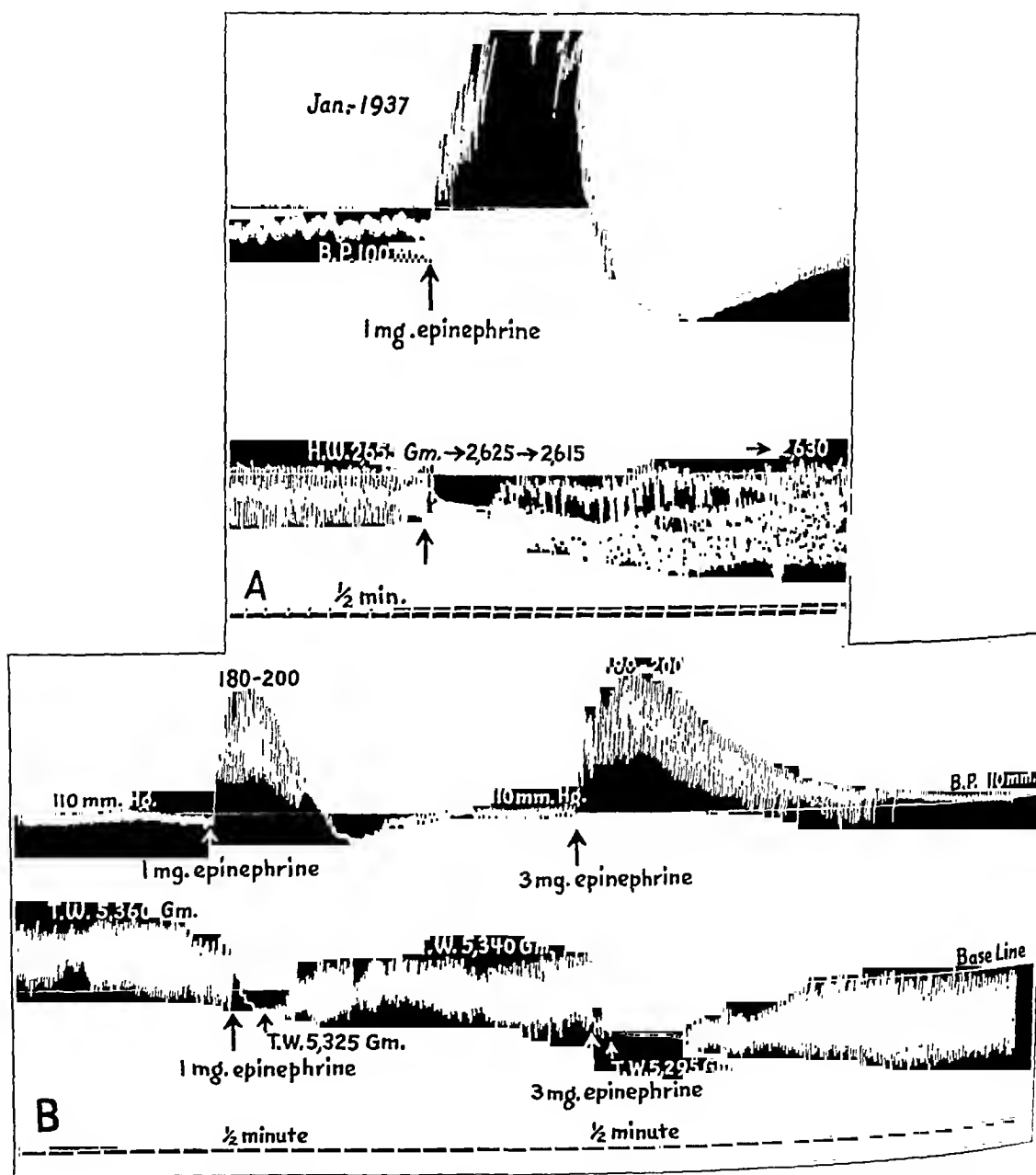
Chart 6.—*A*, influence of epinephrine (1 mg.) on the regional distribution of blood in the head region. *B*, influence of epinephrine (1 to 3 mg.) on the regional distribution of blood in the thoracic region.

amount of splanchnic blood. This increase persists for a longer period (table 15; fig. 7 *B*). The redistribution of blood is to some extent independent of the systolic blood pressure (table 15). It has been

observed that epinephrine in small amounts constricts and in large amounts dilates the blood vessels of the intestine (Hartman and McPhedran [51]). This vasodilatation has been shown to result from its action on the superior mesenteric ganglion and on the dorsal root ganglions of the lower portion of the thoracic region (Hartman, Kilborn and Fraser [52])..

• It is well known that in certain of the viscera the effect of epinephrine is vasoconstrictor no matter how large or how small the dose

TABLE 15.—*Influence of Epinephrine on the Redistribution of Blood in the Splanchnic Area*

Experiment 14		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	170	130	130	130	130
	Splanchnic weight, Gm..	2,600	—225*	—225	—150	—25	+50
Experiment 16							
2 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	125	200	200	140	85	100
	Splanchnic weight, Gm..	2,555	—225*	—125	—75	+175	+175

* Plus sign indicates increase and minus sign loss.

TABLE 16.—*Influence of Epinephrine on the Redistribution of Blood in the Peripheral Area*

Experiment 7		Before Injection	After Injection				
			1 Min.	5 Min.	10 Min.	15 Min.	20 Min.
0.02 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	130	160	95	130	130	130
	Peripheral weight, Gm..	3,590	+62*	+37	+25	+25	+15
Experiment 9							
1 mg. epinephrine hydrochloride	Blood pressure, mm. Hg	115	270	140	65	100	100
	Peripheral weight, Gm..	3,570	+25	—25	—62	+12	+25

* Plus sign indicates increase and minus sign loss.

may be. Such viscera are the spleen (Hartman and McPhedran [51]) and the kidney (Hoskins and Gunning [53]).

In small quantities (0.02 mg.) epinephrine produces a translocation of blood into the peripheral area studied (table 16, fig. 8 *A*), which may

51. Hartman, F. A., and McPhedran, L.: Further Observations on the Differential Action of Adrenalin, Am. J. Physiol. **43**:311, 1917.

52. Hartman, F. A.; Kilborn, L. G., and Fraser L.: Adrenalin Vasodilator Mechanisms, Am. J. Physiol. **46**:502, 1918.

53. Hoskins, R. G., and Gunning, R. E. L.: The Effects of Adrenin on the Distribution of Blood: Volume Changes and Venous Discharge in the Kidney, Am. J. Physiol. **43**:304, 1917.

persist for periods up to one-half hour. In larger doses (1 to 2 mg.) the effect of epinephrine is triphasic. There is an initial increase in weight of the area, followed by a more prolonged decrease and finally a
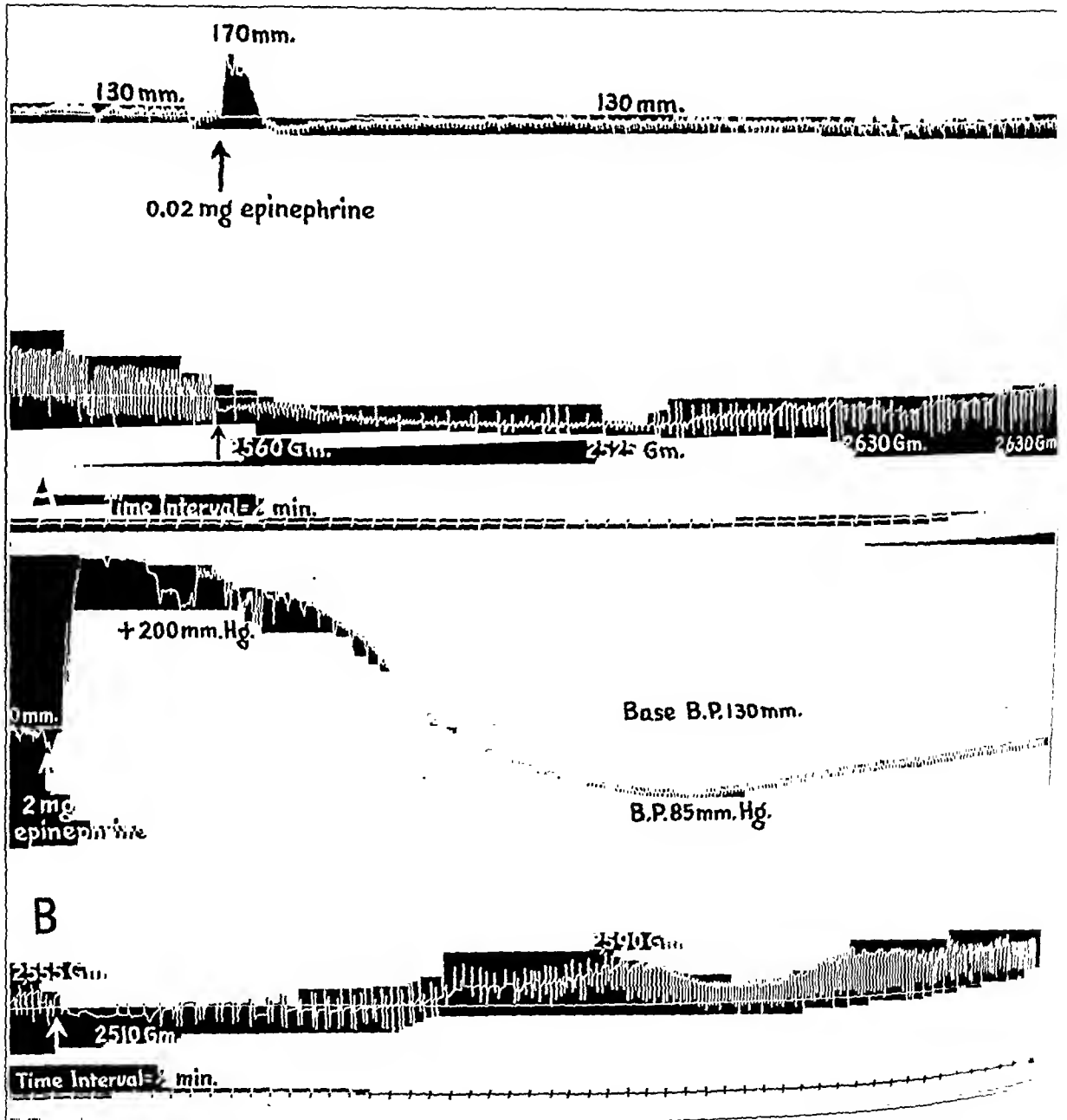
Chart 7.—*A*, influence of epinephrine (0.02 mg.) on the regional distribution of blood in the splanchnic region. *B*, influence of epinephrine (2 mg.) on the regional distribution of blood in the splanchnic region.

terminal slow increase (table 16; 8 *B*). Apparently, the predominant effect of epinephrine, both in small and in large amounts, is to produce a shift of blood into the periphery.
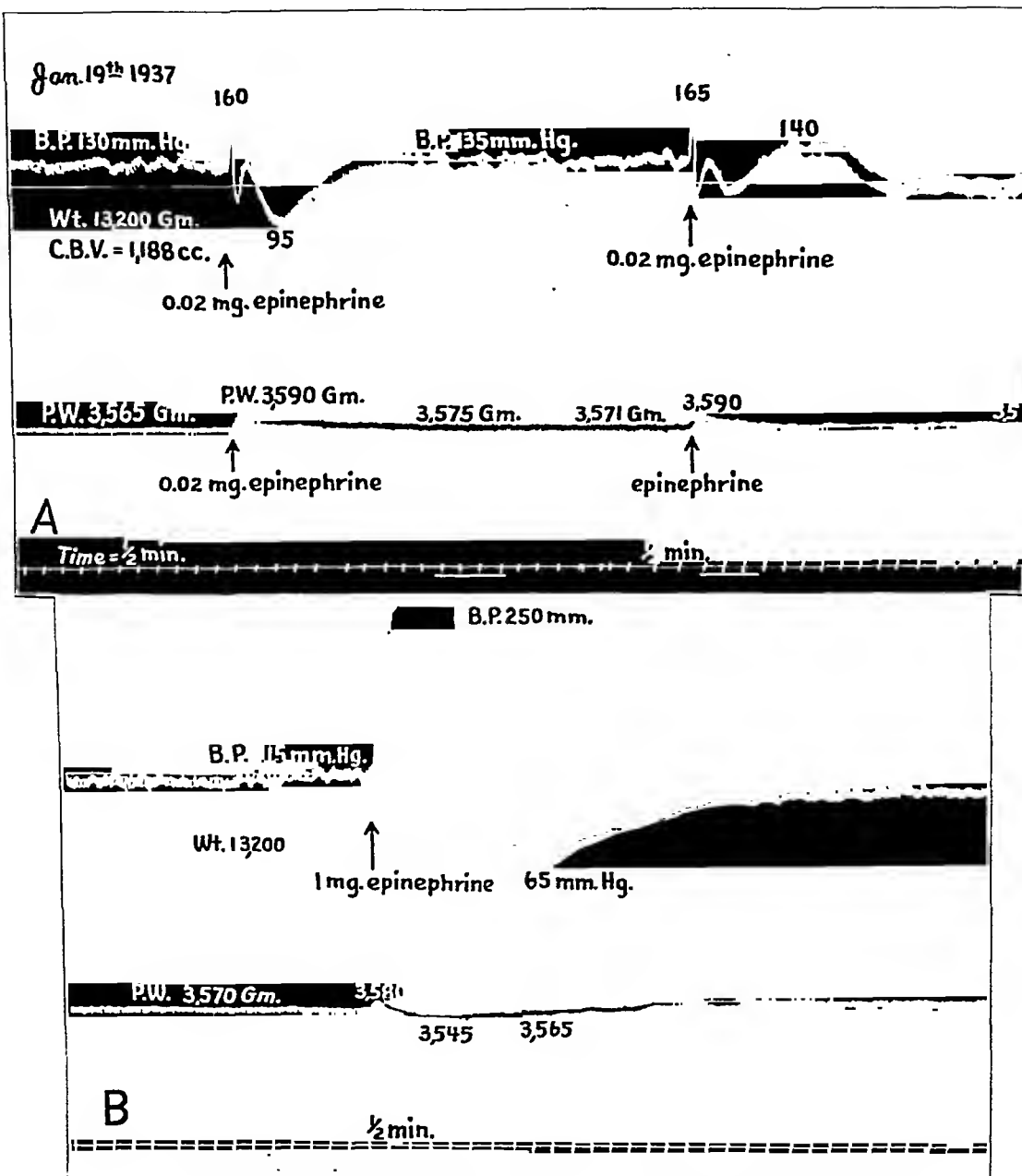
Chart 8.—*A*, influence of epinephrine (0.02 mg.) on the regional distribution of blood in the peripheral region. *B*, influence of epinephrine (1 mg.) on the regional distribution of blood in the peripheral region.

Epinephrine in large or small amounts will produce a constriction of the vessels of the skin (Hoskins, Gunning and Berry [54]). On the contrary, the blood vessels of the muscles are dilated by small amounts (Gunning; [55] Clark [56]) and constricted by large amounts (Gunning [55]). The site of action of epinephrine is believed to be mainly in the capillaries (Dale and Richards; [25] Clark [56]) and possibly also in the arterioles. Vasodilatation caused by epinephrine in the muscles of the hindlimbs results from the action of the substance on the sympathetic ganglions of the lower part of the lumbar and the sacral region and on the dorsal root ganglions of the nerves supplying the hindlimbs (Hartman, Kilborn and Fraser [52]).

COMMENT

This investigation has furnished proof of a striking similarity between the regional redistribution of blood after hemorrhage and that after trauma (Davis [57]). The noticeable feature in both is the excessive shift of blood from the splanchnic area, which seems to act as a reserve depot for blood. In both instances there occurs an early increase of blood in the thoracic area, followed by a decrease. Finally, in both evidence is presented which suggests a late dilatation of the peripheral blood vessels. The impression has been received from these experiments that this peripheral vasodilatation takes place chiefly in the muscles and is merely a passive vasodilatation in response to the excessive splanchnic vasoconstriction. The question is presented: Is this splanchnic vasoconstriction deleterious to the organism? When shock is the result of simple loss of blood the splanchnic vasoconstriction is beneficial and is apparently the chief means whereby the blood pressure is elevated. However, in traumatic shock there is at once established a point of excessive permeability in the vascular system at the site of trauma. Consequently, the effect of splanchnic vasoconstriction is to force more blood into the area of trauma and beyond vasomotor control. In this manner a vicious circle is established. Experiments may be cited to illustrate this point. It has been observed (O'Shaughnessy and Slome [38]) that the induction of spinal anesthesia prolongs the life of an animal in

54. Hoskins, R. G.; Gunning, R. E. L., and Berry, E. L.: The Effects of Adrenin on the Distribution of Blood: Volume Changes and Venous Discharge in the Limb, Am. J. Physiol. **41**:513, 1916.

55. Gunning, R. E. L.: The Effects of Adrenin on the Distribution of Blood: Effect of Massive Doses on the Outflow from Muscle, Am. J. Physiol. **43**:393, 1917.

56. Clark, G. A.: Adrenaline Vasodilatation in Voluntary Muscle, J. Physiol. **84**:344, 1935.

57. Davis, H. A.: Factors in the Production and Treatment of Shock: An Experimental Study, M. Ann. District of Columbia **6**:344, 1937.

a state of traumatic shock. This may be explained readily. Spinal anesthesia, by blocking vasoconstrictor impulses to the splanchnic area, prevents or diminishes the excessive splanchnic vasoconstriction and thus decreases the rate of fluid loss into the site of trauma. Trauma renders an animal sensitive to even a small hemorrhage. It has been demonstrated that the splanchnic vasoconstrictor mechanism becomes increasingly sensitive to each succeeding insult, so that when shock is established even a small hemorrhage may lead to an exaggerated splanchnic vasoconstriction (table 3). Such a "sensitization" takes place after trauma, and the addition of a small hemorrhage will induce, in the same manner, an excessive splanchnic outflow of blood into the site of trauma.

The redistribution of blood following administration of histamine does not resemble that following trauma or hemorrhage and therefore does not lend support to a toxic theory of secondary shock which is based on the release of histamine-like substances from the area of trauma (Cannon and Bayliss [24]). The influence of a small amount of epinephrine (0.02 mg.) on the distribution of blood is similar in many respects to that of hemorrhage and of trauma, i. e., it causes splanchnic vasoconstriction with a shift of blood into the thoracic and the peripheral region. The question arises: Is activity of the adrenal glands necessary for the production of this redistribution of blood? The answer is in the negative, as the same type of redistribution occurs in the adrenalectomized animal (fig. 3 C). The phenomena are dependent, apparently, on the activity of the sympathetic nervous system. An examination of representative data concerning peripheral vasoconstriction reveals that it becomes maximal soon after the reduction in blood pressure (table 4). Thereafter, efforts to maintain the blood pressure appear to depend on vasoconstriction in the splanchnic and thoracic areas.

SUMMARY AND CONCLUSIONS

A simple quantitative and qualitative method is described whereby regional translocations of blood in the intact animal can be recorded graphically. Results of the use of this method in a study of experimental secondary shock are given.

The redistribution of blood following hemorrhages is similar to that following trauma.

Excitation of the sympathetic nervous system with small amounts of epinephrine produces an analogous type of redistribution of blood.

Direct experimental evidence is offered against the occurrence of a splanchnic "pooling" of blood in traumatic and hemorrhagic shock.

The action of histamine on redistribution of blood does not resemble that of hemorrhage, trauma or epinephrine. Emphasis is placed on the

splanchnic vasoconstrictor response, and evidence is presented regarding the importance of exaggeration of this response in hastening the onset of shock after trauma.

Excessive vasoconstriction in the splanchnic and to a lesser extent in the thoracic region forces blood toward the peripheral areas and into any site of abnormal vascular permeability such as might be produced by trauma.

This splanchnic and thoracic vasoconstriction is the direct response to a reduction in blood volume, whether the loss of blood occurs by external hemorrhage or into an area of trauma.

REVIEW OF UROLOGIC SURGERY

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PROSTATE GLAND

Hypertrophy.—Wildbolz [35] pointed out the indications for transurethral resection and for prostatectomy on the basis of 81 cases. He, like most European urologists, has reserved transurethral resection for cases in which there were only moderate changes at the vesical neck and for cases in which the risk of prostatectomy would be excessive. He has removed large, easily bleeding prostate glands by the perineal route.

His results with transurethral resection were gratifying. There were no deaths, and in most cases the patients were in the hospital only a short time. After transurethral resection, 54 patients could empty their bladders completely, while 11 had a sufficient amount of residual urine to make catheterization necessary.

Flocks [36] discussed healing after transurethral prostatic resection performed with the McCarthy resectoscope.

35. Wildbolz, H.: Die Erfolge der transurethralen, elektrischen Prostataresektion bei Prostatahypertrophie, Schweiz. med. Wchnschr. **68**:517-519 (April) 1938.

36. Flocks, R. H.: Local Repair Following Transurethral Prostatic Resection: Its Rôle in the Clinical Events Associated with This Operation, Tr. Southwest. Br., Am. Urol. A., 1937, pp. 26-50.

Destruction of tissue is not more than 3 to 4 mm. in extent and is even. There is no marked increase in evidences of infection below the level of the destroyed tissue.

Epithelization can be expected to be complete in three to four weeks after the operation. Because of this rapid epithelization, scarring is not a prominent feature of repair.

Two facts are of the utmost importance in the understanding of repair and healing after partial prostatectomy: 1. When part of the hyperplastic tissue is removed, dislocation and intraurethral bulging of hyperplastic masses of tissue are caused. 2. The enlarged portion of the prostate gland is supplied, in the main, by the urethral group of arteries, which enter at the prostatic-vesical junction and then course distally through the prostatic tissue. These form the anatomic basis for marked postoperative sloughing and the production of poorly healing masses of tissue bulging into the urethra. The microscopic, gross and cystourethrographic characteristics of these masses were described.

Thompson and Habein [37] reviewed the cases of 1,200 patients 70 years of age or older on whom 1,361 transurethral prostatic resections were performed at the Mayo Clinic. Forty-two per cent of the patients were more than 75 years of age. In order to evaluate the general condition and the cardiovascular-renal status in the entire group of cases, 300 records which were considered to be a fair sample of the whole group were taken at random and were reviewed carefully. It is difficult to express graphically the condition of the patients as far as operative risk is concerned. Approximately 56.6 per cent of the 300 patients whose records were reviewed were considered to constitute risks of grade 3 or 4 (4 is greatest) because of generalized arteriosclerosis, hypertension, coronary disease, myocardial damage or renal insufficiency. For a large number of these patients the risk of suprapubic cystostomy was considered prohibitive. Approximately 36 per cent of the group were considered to constitute risks of grade 2 because of the presence of senile changes, diabetes, past cerebral vascular accidents or hypertension. In only 7.3 per cent of the 300 cases was the classification of minimal surgical risk made. An analysis of renal function in the entire series of 1,200 cases revealed that in 504 (42 per cent) there was a considerable degree of renal damage. Of these 504 patients, 39 per cent had values for urea of from 41 to 100 mg. per hundred cubic centimeters of blood; 24 patients (2 per cent), of from 101 to 200 mg., and 12 patients (1 per cent), more

37. Thompson, G. J., and Habein, H. C.: Transurethral Prostatic Resection: Experience with One Thousand and Two Hundred Patients Seventy Years of Age or More, Proc. Staff Meet., Mayo Clin. **13:**305-311 (May 18) 1938.

than 200 mg. Only 16 (1.3 per cent) of the entire group of 1,200 patients were subjected to preliminary suprapubic cystostomy.

From a review of these cases it is apparent that age and poor general condition no longer prevent surgical relief of urinary obstruction. Comparison of the ages of the patients in any consecutive series of cases in which transurethral resection has been performed with the ages of the patients in any earlier series of cases in which prostatectomy was performed at the Mayo Clinic revealed that ten times as many men more than 75 years of age are now submitting to operation for relief from urinary obstruction as when suprapubic prostatectomy was the operation of choice.

Carcinoma of the prostate gland is found in about 20 per cent of cases. By transurethral resection the obstructing tissue can be removed, which permits the patient to void urine comfortably and normally for as long as five or six years. Recurrences of urinary obstruction sometimes necessitate subsequent operation, and up to the present time no patient has chosen suprapubic drainage in preference to a second transurethral resection.

Thompson and Habein [37] emphasized the importance of careful preoperative survey of the cardiovascular system. Recent coronary occlusion and myocardial infarction demand postponement of operation for two to three months except in cases of great emergency. Substernal pain on exertion, paroxysmal nocturnal dyspnea and recurrent attacks of pulmonary edema are cardinal signs of coronary sclerosis and serious myocardial damage. Old persons do not tolerate digitalis well, and its use is restricted until definite indications are present, such as congestive heart failure with auricular fibrillation and edema.

The first consideration in the treatment of renal insufficiency resulting from urinary obstruction is the establishment of adequate drainage. This is best accomplished by the use of an inlying urethral catheter. The second most important consideration is the administration of ample quantities of fluid, an average of 3,000 to 4,000 cc. daily; in exceptional cases as much as 7,000 cc. daily may be advisable. In the presence of normal values for blood chlorides, a 5 or 10 per cent solution of dextrose may be chosen. Excessive use of physiologic solution of sodium chloride may lead to increased renal damage or may result in edema. Study of the carbon dioxide–combining power of the blood aids in recognition of the acidosis which may accompany renal insufficiency. Under these conditions, marked improvement in renal function frequently follows administration of appropriate alkaline solutions.

Spinal anesthesia is usually the best type of anesthesia for the elderly patient with prostatic obstruction. Fifty milligrams of procaine hydrochloride injected into the third lumbar interspace generally is sufficient. It is important that the operation be of short duration.

Extreme loss of blood and shock may occur if it is prolonged more than forty-five minutes. Thompson prefers to perform the operation at two sittings rather than to prolong a single operation unduly and to run the risk of dire consequences. Fall in blood pressure should be prevented by appropriate measures, or, if it occurs, the pressure should be restored as soon as possible. In the majority of the 1,200 cases the Thompson resectoscope was employed. With this instrument, usually 2 Gm. of tissue can be removed in each minute of the operation. At the conclusion of the operation a hemostatic bag may be inserted. Thompson and Habein expressed the belief that it is important for the patient to be out of bed the day after prostatic resection if possible. This plan, they feel, prevents cardiovascular complications. Of this series of 1,200 patients, 70.4 per cent did not have a temperature higher than 100 F. at any time during postoperative convalescence. With careful preoperative preparation and postoperative care and with increased experience and refinements in surgical technic, the scope of transurethral prostatic resection has so broadened that few patients are denied surgical relief of urinary obstruction. The mortality rate among the 1,200 patients, all of whom were more than 70 years of age, was 1.6 per cent.

Thompson [38] reviewed a series of 100 consecutive cases in which prostatic resection was performed in 1937 and compared the details of management with those in a similar series of 205 cases, reviewed in 1932. During the time the series of 205 patients was accumulating in 1932, 37 additional patients underwent suprapubic prostatectomy; therefore, in 84.7 per cent of cases transurethral operation was performed, while in 15.3 per cent the prostate gland was removed by open operation. During the time when the 100 consecutive patients were being treated in 1937 no patient was advised to have any form of operation except transurethral resection. The patients operated on in 1937 were older, on an average, than those operated on in 1932. In 1932, when the technic of transurethral resection was relatively imperfect, suprapubic drainage was employed in 17.5 per cent of the 205 cases. In 1937 preliminary cystostomy was not performed at the Mayo Clinic in any of the 100 cases. In 4 cases, however, cystostomy had been performed elsewhere.

In 1937 preoperative drainage of the bladder by inlying urethral catheter was employed in only 17 per cent of cases, although intermittent catheterization frequently was employed until completion of a general medical examination, transurethral resection being performed

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38. Thompson, G. J.: Clinical Data Concerning Prostatic Resection, J. Urol. **40**:121-128 (July) 1938.

at the same time. The decrease in complications and febrile reactions seemed to justify this practice.

If a patient has advanced uremia, it is usually best to employ an inlying catheter; however, one should aim to rid the patient of the catheter at the earliest possible moment. Transurethral prostatic resection gradually is becoming a more thorough operation than it was formerly, as is evidenced by the figures which show, in the series of 1932, that there were only 5 cases (2.4 per cent) in which 25 Gm. or more of tissue were removed, whereas in the series of 1937, 46 per cent of cases fell into this category.

Of the series of patients operated on in 1932 with the Braasch-Bumpus punch, 10.5 per cent required a second or a third operation, whereas in the series of 1937, in which operation was done with the Thompson resectoscope, 4 per cent of the patients needed a second resection and none required three operations.

Thompson discussed some of the important details of surgical technic. Thorough postoperative drainage of the bladder through the inlying catheter is considered of great importance. Thompson does not employ a hemostatic bag routinely. Careful observation and aseptic technic in the handling of catheters and in postoperative lavage of the bladder are of paramount importance. He does not advise the routine employment of urinary antiseptics during the early postoperative period.

In the 1932 series of patients, 43 per cent had a postoperative temperature of more than 101 F., whereas in 1937 this degree of febrile reaction occurred in only 9 per cent. Epididymitis occurred postoperatively in 8 per cent of the cases in 1932 and in only 1 per cent of the series of 1937. Bilateral partial vasectomy was performed in 16 per cent of the cases in 1937. The period of hospitalization in 1937 was definitely shorter than in 1932. There was no mortality in either series. During the years 1931 to 1936 inclusive, Thompson performed approximately 1,800 prostatic resections, with 12 deaths. a mortality of less than 1 per cent.

Walther and Willoughby [39] stated that prostatic hyperplasia can no longer be regarded as an independent entity; it is inseparably bound up with endocrine changes affecting the pituitary body and the testis.

In cases of early prostatism or in cases in which some serious physical disability accompanies any type of prostatic obstruction and surgical operation therefore seems inadvisable, the androgens should be given conscientious trial. The disadvantage of this mode of treatment is that, as with insulin, a maintenance dose must be continued; therefore, contact with the patient is necessary for an indefinite period, and massage usually is indicated.

39. Walther, H. W. E., and Willoughby, R. M.: Hormonal Treatment of Benign Prostatic Hyperplasia, J. Urol. **40**:135-144 (July) 1938.

Preparations of androsterone and of testosterone propionate for oral and intramuscular use are available.

Using these substances, Walther and Willoughby have treated 15 patients with benign prostatic hyperplasia during the past two years, with resulting clinical improvement.

Cancer.—Semans [40] reported a case of carcinoma of the prostate gland with metastasis in the testis. `

The metastatic growth in the testis was too small to be felt on physical examination and was first found on microscopic examination of a routine section of the testis.

In many sections of the cord no trace of the tumor could be seen. The assumption is therefore that the cells came by way of the arteries leading to the testis. The tumor cells in the veins and lymphatic structures of the testis may have arisen from the tumor tissue lying among the seminiferous tubules.

Of the 140 cases of primary carcinoma of the prostate gland indexed in the files of the Johns Hopkins Hospital, the tumor involved by extension the pelvic lymph nodes in 43 cases, the bladder in 31, the seminal vesicles in 21 and the rectum in 8. Metastatic growths were found in the lungs in 26 cases; in the osseous system in 18; in the retroperitoneal, mediastinal and bronchial lymph nodes in 16; in the liver in 12; in the ureter in 7; in the pleura in 5; in the adrenal glands in 5; in the diaphragm in 4; in the peritoneum in 3, and in the pancreas in 2. The vas deferens, the urethra and the kidney were each involved in 1 instance.

URETHRA

Prolapse.—Berry and Greene [41] stated that prolapse of the urethra is an entity in the field of urology which, although uncommon, is most often seen in young girls.

Circular amputation of the prolapsed mucosa is a satisfactory form of treatment. Gynecologists who have used this method report no recurrence. Possible hemorrhage is adequately controlled by an inlying catheter.

The argument that stricture may result from the amputation is reduced in importance when the ease with which stricture can be prevented by timely postoperative dilation of the urethra is considered.

The simplicity of the circular amputation operation with the radio knife in itself has much to recommend its use in cases of prolapse of the mucous membrane of the urethra. Recognition of the fact that

40. Semans, J. H.: Carcinoma of the Prostate with Metastasis in the Testis, J. Urol. **40**:524-529 (Oct.) 1938.

41. Berry, N. E., and Greene, H.: Prolapse of the Female Urethra, J. Urol. **39**:92-96 (Feb.) 1938.

prolapse is chiefly due to redundancy of the mucosa and the fact that the operation is effective certainly justify its use.

Stone.—Stoccada [42] reported the case of a man aged 66 who had carried a gonococcic infection for more than forty years. There was a diverticulum behind a urethral stricture in which was pocketed a stone which had not caused symptoms. The stone weighed 155 Gm. and was composed mostly of phosphates.

GENITAL TRACT

Tuberculosis.—Menville and Priestley [43] reported their study of tuberculosis of the male genital tract in 62 cases in which postmortem examination had been performed. The average age of the patients at death was 43.9 years. Trauma and infection seemed of slight, if any, etiologic significance.

For practical purposes, tuberculous lesions in the genitalia should always be considered secondary to tuberculous foci elsewhere in the body (96.8 per cent). In this study, lesions elsewhere in the body were observed most often in the kidney (51.6 per cent) and less often in the lymph nodes, lungs and other organs. Miliary tuberculosis is frequently a terminal event in cases of genital tuberculosis in which death occurs. Lesions were found in the genitalia in the following order of frequency: prostate gland, epididymis, seminal vesicle and testis. If renal tuberculosis is present the prostate gland is almost always involved; this is not equally true of the epididymis. If renal tuberculosis is not present the epididymis is frequently involved, although the prostate gland may be normal. The route of infection and the actual pathologic relation of involvement in one part of the genital tract to involvement in another are in many cases difficult to determine.

Wells [44] contended that tuberculous epididymitis is always secondary to tuberculosis of the urinary tract and therefore that every patient who has tuberculous epididymitis should be suspected of having renal tuberculosis.

The path of invasion is as follows: from the blood stream to the kidney, from the kidney to the bladder by the urinary stream and from the posterior portion of the urethra to the epididymis by the lumen of the vas deferens. Wells based his conclusions (1) on clinical evidence in 55 cases, (2) on an analogy to pyogenic epididymitis and (3) on reasoned deductions from established facts.

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42. Stoccada, F.: Calcolo gigante dell'uretra posteriore, Schweiz. med. Wchnschr. **68**:859-860 (July 16) 1938.

43. Menville, J. G., and Priestley, J. T.: Tuberculosis of the Male Genital Tract: A Pathologic Study, J. Urol. **40**:66-73 (July) 1938.

44. Wells, C. A.: Tuberculous Epididymitis, Brit. J. Urol. **10**:114-130 (June) 1938.

Epididymectomy is the operation of choice for tuberculous epididymitis. Because of the frequency of subsequent infection of the opposite side, under certain circumstances the vas on the healthy side may be ligated and divided. This operation prevents contralateral involvement and should be done (*a*) when the patient is old, (*b*) when one testis has been completely destroyed or needlessly sacrificed and (*c*) in the presence of frank prostatitis and vesiculitis. In the absence of epididymitis vasoligation is reasonable when urinary tuberculosis is present.

Seminal Vesiculitis.—Peterson [45] stated that seminal catheterization is advocated as a practical, painless and nontraumatic procedure if properly done on a prepared patient.

On injection, the vesicle fills first, the ampulla next and the vas deferens last. The explanation of this phenomenon is to be found in the law that liquids flow in the direction of least resistance, which also explains why injection into the ampulla and vas deferens cannot be made if the catheter does not fit the ejaculatory duct, leaving the way open for the dye to regurgitate.

The presence of valves in the ampulla or the assumption that tonic closure of the ampulla takes place could not be substantiated.

Dilation of the ejaculatory ducts or injection of the seminal tract should be followed by ejaculation within two to three hours in order to promote drainage and prevent epididymal complications.

Vesiculograms made after injection of suitable contrast material reflect the size, shape and structure of the seminal vesicles as well as the relative topographic relation of the ampullae and the vasa deferentia.

Vesiculograms showing the characteristics of the normal vesicle and various types of pathologic vesicles obtained through retrograde catheterization were offered.

Improvement in the drainage and structure of the seminal vesicles, obtainable through retrograde catheterization of the ejaculatory ducts, was proved roentgenographically.

URINARY INFECTIONS

Helmholz [46] gave the essentials of diagnosis and treatment of infections of the urinary tract in infancy and childhood.

In the consideration of urinary antiseptics there is a wide choice, but in the last analysis two drugs stand out prominently above the rest, namely, mandelic acid and sulfanilamide. Sulfanilamide has a number

45. Peterson, A. P.: Retrograde Catheterization in Diagnosis and Treatment of Seminal Vesiculitis, J. Urol. **39**:662-677 (May) 1938.

46. Helmholz, H. F.: Urinary Infections in Infancy and Childhood: Diagnosis and Treatment, J. A. M. A. **111**:1719-1722 (Nov. 5) 1938.

of advantages over mandelic acid: It can be given in the acute stage of the infection; its bactericidal effect is not entirely dependent on the reaction of the urine, and it is excreted in bactericidal quantities by kidneys that are severely injured.

Administration of sulfanilamide does not offer any special difficulties. It is taken readily by infants and older children by mouth, and when it is not tolerated because of gastric irritability it can be given subcutaneously or intravenously. Its use in the acute stages of the infection, especially in infants, is a definite advance over the previous use of only diuresis and alkalization.

In infections caused by Proteus ammoniae the urine is strongly alkaline. In the treatment of this type of infection sulfanilamide is the drug of choice because of its superior action on alkaline urine and because of the difficulty in bringing the urine into the acid range necessary for the bactericidal action of mandelic acid or methenamine.

A particular advantage of sulfanilamide, which deserves emphasis, is the possible concentration that is bactericidal in the urine of patients who have injured the kidneys. It has been Helmholz' experience with the ketogenic diet and with methenamine and mandelic acid that an injured kidney cannot secrete a urine of low p_H, and even in cases in which the concentration of urea in the blood is normal the injured kidney cannot be beneficially influenced because of this difficulty. It is striking, therefore, that sulfanilamide can be excreted in the urine in sufficient concentration in cases in which the concentration of urea in the blood is well above normal.

Sulfanilamide is given in two-thirds the usual dose for streptococcic infections; that is, 10 grains (0.65 Gm.) per 20 pounds (9 Kg.) of body weight is given daily. From four to six doses are given daily. Sodium bicarbonate is given in doses of from 30 grains (2 Gm.) to 60 grains (4 Gm.) a day. Water usually is given in the usual amounts, but the intake of fluids can be restricted if the concentration of sulfanilamide in the urine remains low. A concentration of 50 mg. of the drug in its free form in 100 cc. of urine usually is secured from this dose. After the urine has become sterile it is essential to keep it so for four to six days and then to discontinue medication. After four days cultures are again made, to ascertain that the urine has remained sterile. In a number of cases concentrations of half this amount have brought about sterilization of the urine. When the drug has been administered in this manner it has only exceptionally given rise to cyanosis, and in Helmholz' experience it never has caused agranulocytosis or anemia.

The field of usefulness of mandelic acid has been narrowed considerably by the introduction of sulfanilamide, but the former drug still is useful, not only for streptococcic infections but because of its

effect on all bacteria, cocci and bacilli alike; when a proper concentration of the acid in the urine and a proper p_H of the urine are obtained it is a most dependable drug. As determined in vitro and therapeutically, it acts equally well in bacillary and in coccic infections.

Mandelic acid is administered as the elixir of ammonium mandelate or as ammonium mandelate in suppositories. It is given in doses that will produce a concentration of from 0.5 to 1 per cent of the drug in the urine. At the Mayo Clinic, Helmholz administers 1 Gm. for each 100 cc. of urinary output in the twenty-four hours. As most of the mandelate is excreted in the urine, a concentration of approximately 1 per cent results.

McMartin, Schmitz and McMartin [47] stated that most ambulatory patients cannot tolerate more than 20 to 40 grains (1.2 to 2.5 Gm.) of sulfanilamide daily. On account of the many severe phenomena that may follow its administration, such as variable grades of dermatitis and anemia, it should be dispensed on nonrefillable prescriptions. Old persons do not tolerate the drug as well as do young persons.

Sulfanilamide is not of much value in treatment of infections of the upper part of the urinary tract or of the bladder when drainage is insufficient or when calculi are present. The response of acute gonorrheal infections is best if patients have sought treatment at the first appearance of the discharge. Delay of a few days usually means a longer time before a sterile smear is obtained. The drug has been found to be specific against infections with Bacillus coli if drainage is sufficient and if calculi are not present.

All subjective symptoms caused by the drug disappear shortly after its administration has been stopped.

Cook [48] stated that mandelic acid is most efficacious under the following conditions: (1) when the urine is brought into direct and continued contact with the infected surface; (2) when the infection is largely superficial; (3) when there are no marked cicatricial changes in the renal tissues as a result of long-standing infection; and (4) when there is no obstruction to the drainage of urine. When the drug is administered in adequate doses (32 cc. of the syrup daily or 48 cc. of the elixir of mandelic acid daily) uncomplicated bacillary infections of the urinary tract will be cleared up in 90 per cent of cases. Occasionally two courses of treatment are necessary. Cocci, as a rule, are not affected by this form of therapy, with the exception of Streptococcus faecalis. When chronic prostatitis is associated with urinary

    47. McMartin, C.; Schmitz, W. H., and McMartin, W. J.: Use of Sulfanilamide in Genito-Urinary Infections, J. Urol. **40**:233-238 (July) 1938.
    48. Cook, E. N.: Chemotherapy in Infections of the Urinary Tract, J. Urol. **39**:692-698 (May) 1938.

infection the results with mandelic acid are not so good until the prostatitis has been eliminated.

When renal function is not good, mandelic acid must be administered with care. Nausea and (sometimes) vomiting are the most common complications following the use of mandelic acid. In 1 to 2 per cent of cases microscopic hematuria is noted, and occasionally gross hematuria may follow administration of this drug.

Recently sulfanilamide has been more widely used than before in treatment of infections of the urinary tract. The usual procedure is to give 60 grains (3.8 Gm.) each day for two or three days, then to reduce to 40 grains (2.5 Gm.) daily for the remainder of the treatment, which is continued generally for eight to fourteen days. This treatment may be repeated if necessary. For elderly patients the initial dose is 40 grains daily. In treatment of gonorrheal infection a larger dose is required.

Sulfanilamide will eradicate at least 90 per cent of uncomplicated infections of the urinary tract, and it is of value in treatment of infections with organisms of the genus Proteus. Fortunately, when sulfanilamide is used it is not necessary to depend on any particular p_H of the urine, although a dose of 10 grains (0.65 Gm.) of sodium bicarbonate usually is given with each dose of sulfanilamide. Complications associated with infections of the urinary tract usually decrease the efficacy of sulfanilamide as well as of other drugs; however, in cases of chronic prostatitis associated with bacillary infection the results obtained with sulfanilamide have been encouraging. Frequently, chronic prostatitis has disappeared in ten to fourteen days with this form of treatment. Sulfanilamide is not as effective against coccic as against bacillary infections, but it is definitely worth while. Headache, vertigo and lassitude occur almost invariably with the use of sulfanilamide. Fever, cyanosis or cutaneous eruption may also occur. Cook emphasized the importance of close observation, careful administration of the drug and careful regulation of the dose.

Vest, Harrill and Colston [49] stated that the introduction of sulfanilamide is the most important forward step yet made in the treatment of gonorrhea and other infections of the urinary tract.

Sulfanilamide may be only the forerunner of far more efficacious and satisfactory compounds, but with the vast problems yet to be elucidated concerning sulfanilamide itself years undoubtedly will be required to produce results such as Ehrlich predicted. From research in all fields, however, whether chemical, biologic or clinical, undoubtedly there will evolve the ideal remedy postulated by Ehrlich in 1913: "a remedy entirely innocuous in itself, which is not fixed by the organs

49. Vest, S. A.; Harrill, H., and Colston, J. A. C.: The Use of Sulfanilamide in Urological Infections, Tr. Southwest. Br., Am. Urol. A., 1937, pp. 127-150.

of the body but which would, however, strike the parasites with full intensity."

Hutchison [50] reported a series of 35 consecutive cases from the ward for venereal diseases in the Belvedere Hospital, between January 1935 and March 1938. The first 12 patients were treated with local applications only, the second 12 with a stabilized suspension of Ducrey bacilli (Dmelcos vaccine) and the remaining 11 with sulfanilamide. Each patient had a definite bubo, and some had a chancroid on the penis. None suffered from gonorrhea, and the blood serum of all gave a negative Wassermann reaction.

Treatment in all 35 cases was successful, and the most striking difference among the three groups was the reduction in the average duration of hospitalization from forty-six days to fifteen days. Of the 24 cases in which sulfanilamide was not given, aspiration was necessary in 20 and incision in 18. Of the 11 cases in which sulfanilamide was given, aspiration was required in only 2 and incision in none.

Although the number of patients so far treated with sulfanilamide is small, the evidence favors use of this drug in the treatment of bubo.

GLANDULAR THERAPY

With the use of gonadotropic substance from the urine of pregnant women, Thompson, Heckel and Bevan [51] have produced descent of 8 of 36 undescended testes (22 per cent) of 28 patients, varying in age from 1½ to 37 years.

By exclusion of 7 patients who were more than 15 years of age the incidence of successful results rose to 33 per cent. Testicular descent was not produced in any case if the patient was more than 12 years of age.

In all cases in this series in which descent took place, the testis was in the inguinal canal or at a lower level before treatment was started. In all successful instances in which the data were extensive enough to warrant conclusions, descent occurred within nine weeks.

In 8 cases in which operative procedures were carried out, after prolonged treatment with this material had failed to produce descent, anatomic factors which prevented descent were found. Even when descent did not occur, administration of the material, by increasing the size of the parts involved, seemed to make subsequent operative procedures less difficult.

50. Hutchison, A.: Treatment of Bubo with Sulphanilamide, Lancet **1**:1047-1048 (May 7) 1938.

51. Thompson, W. O.; Heckel, N. J., and Bevan, A. D.: Influence of Anterior Pituitary-Like Principle on External Genitalia of Young Boys, J. Urol. **40**:145-153 (July) 1938. The preparation used was follutein (Squibb).

A striking result of the treatment was an increase in the size of the genitalia, which occurred in more than half the cases and was marked in more than a third. This increase was occasionally so marked that changes simulating premature puberty resulted.

Excessive genital growth may be prevented by avoiding long-continued treatment and by careful observation of the patient. Some regression in the size of the genitalia may occur when treatment is stopped.

Because of its stimulation of genital growth the material is also of value for use before operation for hypospadias, after operation for undescended testis when the testis has not been brought to a sufficiently low level and in the treatment of hypogenitalism.

Vest and Howard [52] reported the use of testosterone propionate in 6 cases of hypogonadism and in 2 cases of prepubertal boys. It seems to constitute a satisfactory replacement therapy for hypogonadism of the male human being. The authors have shown that it produces profound anatomic changes, resulting in the proportionate growth of the phallus, scrotum, seminal vesicles and prostate gland, as well as in development of hair in the pubic region, in the axillas and on the extremities. Other results have been laryngeal changes, the appearance of considerable prostatic secretion, ejaculation with coitus and marked changes in the skin. There have been, in addition, changes in general appearance and improvement in personality. Administration of the material has induced libido and potentia in cases in which these had not existed previously and has restored normal sexual life to a patient who was impotent after castration. No evidence of increase in tolerance to the drug has been noted.

PROGNOSIS OF UNILATERAL NEPHRECTOMY

Deming [53] stated that the expectancy of life of the unilaterally nephrectomized person depends (1) on the cause for which the kidney was removed, (2) on the condition of the remaining kidney and (3) on the social status of the patient. Certain operative procedures applicable in cases in which tuberculous or pyogenic infection exists are available; these procedures diminish the mortality and shorten the postoperative course. The young person whose kidney has been removed for other causes than malignant tumor has a normal expectancy of life. Marriage is permissible for those persons whose kidneys func-

52. Vest, S. A., Jr., and Howard, J. E.: Clinical Experiments with the Use of Male Sex Hormones. J. Urol. **40**:154-183 (July) 1938.

53. Deming, C. L.: The Future of the Unilaterally Nephrectomized Patient, J. Urol. **40**:74-82 (July) 1938.

tion normally for a reasonable period after nephrectomy. Pregnancy is permitted for all healthy women who have not harbored a malignant growth.

UROGRAPHY

Praetorius [54] called attention to the fact that the blood clots can be impregnated by weak solutions of silver nitrate, such as might be used for lavage of the renal pelvis. Blood clots occasionally are a source of error in roentgenologic diagnosis, for they may be mistaken for stones. Several roentgenograms illustrated this.

Lateral pyelograms in 3 cases of perinephric abscess reported by Menville [55] showed a uniform anterior arclike displacement of the kidney and ureter on the affected side. Postoperative lateral pyelograms in the same cases disclosed that the kidneys and the ureters were in normal position and that there was no evidence of anterior displacement. A lateral pyelogram in a case of very early perinephric abscess gave evidence of minute, anterior displacement of the kidney and ureter.

Stevens [56] discussed roentgen examination of the kidney, with special reference to back flow and to injuries associated with retrograde pyelographic examination.

He stated that excretory urographic study furnishes sufficient data for exact diagnosis in a limited number of cases; in the others it must be supplemented by retrograde injections. The better visualization of the renal cortex after excretory as compared with that after retrograde urographic study is an important factor in the diagnosis of tumors of the kidney that do not involve or exert pressure on the renal pelvis or calices.

It is impossible to perforate a normal renal pelvis with an ordinary ureteral catheter. Extreme gentleness should be employed in catheterization of, and in injection into, the renal pelvis of infants and young children. Injury to the kidney and back flow are not uncommon in the course of retrograde pyelographic examination. Filling the renal pelvis to the point of discomfort is sometimes a dangerous procedure. The principal danger accompanying extravasation into the parenchyma of the kidney and in the various types of back flow lies in dissemination of infectious material. Extravasation into the renal parenchyma may

54. Praetorius, G.: Eine Irrtumsquelle bei Röntgenuntersuchungen der Niere, Ztschr. f. Urol. **32**:350-355, 1938.

55. Menville, J. G.: The Lateral Pyelogram as a Diagnostic Aid in Perinephric Abscess, J. A. M. A. **111**:231-233 (July 16) 1938.

56. Stevens, W. E.: Roentgenologic Examination of the Kidney with Special Reference to Backflow and Injuries Associated with Retrograde Pyelography, Tr. Am. A. Genito-Urin. Surgeons **30**:169-182, 1937.

be responsible for mistakes in diagnosis. Rupture extending through the capsule of the kidney is the most dangerous complication associated with retrograde pyelographic examination.

MULTIPLE MALIGNANT GROWTHS

Kretschmer [57] reported in detail 5 cases of multiple primary malignant tumor. In 3 cases the multiple tumors were in the urogenital tract, and in 1 case one was in the prostate gland and the other on the ear. In the first case 3 primary malignant tumors were present. Studies seem to indicate that the incidence of such tumors is greater in the United States than in Europe.

FORMATION OF BONE IN TRANSPLANTS FROM THE UROGENITAL TRACT

Abbott, Goodwin and Stephenson [58] found that the epithelial lining of the canine kidney, renal pelvis, ureter or any portion of the vesical mucosa (with the exception of that which covers the vesical trigon) when transplanted to a position within the sheath of the rectus abdominis muscle produced an epithelium-lined cyst, in connection with which true bone was formed.

The epithelial lining of the fundus of the bladder of the cat when transplanted in the same manner produced large, thin-walled cysts. Formation of bone did occur, but to a much less degree than when the dog was the experimental animal.

Epithelial transplants from the fundus of the bladder of a rabbit produced cysts but no bone.

Vesical mucosa from the fundus of the bladder of the guinea pig produced masses of epithelium, associated in 2 cases with formation of bone.

The mucous membrane of the vas deferens, fallopian tubes, uterus, vagina and rectum when transplanted produced cysts lined by their own particular type of epithelium but did not produce bone.

Removal of three parathyroid glands appeared to inhibit formation of bone after transplantation of epithelial grafts from the fundus of the bladder of the dog. This could be corrected by administration of calcium.

The investigators' results, therefore, demonstrate that the bone-forming potentiality of the various epithelial transplants cannot be assigned to sets of embryologic derivatives but should be attributed to

57. Kretschmer, H. L.: Multiple Primary Cancers, J. Urol. **40**:421-445 (Sept.) 1938.

58. Abbott, A. C.; Goodwin, A. M., and Stephenson, E.: Heterotopic Bone Formation Produced by Epithelial Transplants from Urogenital Tract of Dogs, Rabbits, Guinea-Pigs and Cats. J. Urol. **40**:294-311 (Aug.) 1938.

different types of epithelium: transitional epithelium can grow bone (renal pelvis, ureter and bladder); columnar epithelium (vas deferens, tubes, uterus and rectum) and stratified squamous epithelium (vagina) cannot.

DIABETES IN UROLOGIC SURGERY

Duff and Williams [59] stated that the patient in whom a genitourinary disturbance is complicated by diabetes should be cared for by a urologist and also by an internist, so that there will be good management of the patient's diet. Dehydration and severe ketosis are the only contraindications to urgent surgical operation. Absolutely sugar-free urine and low values for blood sugar are not essential before operation. The type of diabetes encountered in urologic practice usually is mild, and deaths should not be of diabetic origin. Insulin should be used cautiously, mainly for the purpose of combating dehydration and ketosis and to control severe glycosuria. If it is given until the urine is free of sugar and the value for blood sugar is low, it may cause dangerous hypoglycemia.

UROLOGIC DIAGNOSIS

Illustrative cases emphasize the fact that lesions of the urinary tract sometimes produce symptoms strongly suggestive of intra-abdominal disease.

Chute and Kelley [60] stated that this is not an everyday occurrence but added that it happens with sufficient frequency to make it advisable that the possibility of some pathologic condition of the urinary tract be kept in mind in the study of cases in which there are abdominal symptoms and the diagnosis is doubtful. In a fair number of Chute and Kelley's cases urinalysis and plain roentgenograms gave negative results. Therefore, since few patients are too ill to tolerate intravenous urographic examination this procedure and further urologic study, if indicated, should be carried out in any puzzling case in which abdominal symptoms are present even though urinalysis and plain roentgenograms do not give evidence of abnormality.

ADRENAL TUMORS

Walters and Kepler [61] reported 7 consecutive cases of tumor of the adrenal cortex in which recovery occurred after removal of the tumor. Symptoms produced by a tumor of the adrenal cortex depend on the

59. Duff, J., and Williams, F. W.: Diabetes in Surgical Urology, J. Urol. **40**: 446-451 (Sept.) 1938.

60. Chute, R., and Kelley, S. B.: Lesions of the Urinary Tract Producing the Symptoms of Intra-Abdominal Disease, J. Urol. **39**:683-691 (May) 1938.

61. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment; A Study of Seven Operated Cases, Ann. Surg. **107**:881-896 (June) 1938.

sex and age of the patient at the time the tumor begins to function. These tumors are encountered most frequently among women and are characterized by variable changes in secondary sexual characteristics, such as cessation of menstruation, occasional hypertrophy of the clitoris, abnormal growth of hair of masculine distribution and characteristic lesions of the skin, such as a florid complexion accompanied by acne and purplish striations. In girls, tumors of the adrenal cortex tend to produce precocious puberty, more masculine than feminine in character. The disease seldom occurs among males. The clinical picture is not pathognomonic. Similar clinical pictures may result from certain tumors of the gonads, from hyperplasia of the adrenal cortex with or without thymic tumors and from various intracranial lesions not directly involving the pituitary body.

Routine laboratory studies have been of little aid in differential diagnosis, although the presence of a high concentration of estrogenic substance in the urine is suggestive of carcinoma of the adrenal cortex provided pregnancy is excluded. Injection of air about the adrenal gland has been of aid in localizing some adrenal tumors in some cases.

MacKenzie and McEachern [62] reported a case of paroxysmal hypertension due to adrenal pleochromocytoma. The patient, a man 29 years of age, had suffered from attacks of increasing severity for eighteen months. The attacks lasted two to ten minutes and were characterized by nausea, substernal distress, generalized and localized headache, tremor, pallor and numbness of the extremities. They were followed by exhaustion. Attacks were produced by exercise, change of posture and abdominal massage. They were intensified during fasting and were relieved by taking food. During an attack there were a great rise of the brachial and retinal blood pressure, slowing of the cardiac rate, disappearance of the radial pulse, drop in cutaneous temperature, increase in the number of lymphocytes in the blood stream and glycosuria. In the intervals between attacks the blood pressure was normal and there was no evident cardiovascular abnormality. Plain roentgenograms, intravenous pyelograms and massage over the adrenal glands failed to demonstrate the site of the tumor.

Exploration of the region of the left adrenal gland did not reveal a tumor. At the same sitting the opposite side was explored, and an encapsulated tumor of the weight of a golf ball (24 Gm.) was removed from the right adrenal medulla. It proved to be a typical pleochromocytoma, and an extract of it contained a large amount of epinephrine.

62. MacKenzie, D. W., and McEachern, D.: Tumor of Medulla of Adrenal (Adrenal Pleochromocytoma) with Removal and Relief of Paroxysmal Hypertension, J. Urol. **40**:467-476 (Oct.) 1938.

Further attacks did not occur after operation, and four and one-half months later the patient reported himself entirely well.

Review of the literature showed that some 20 patients have been operated on; including the 1 whose case was reported by MacKenzie and McEachern, 5 died from shock or complications. Fifteen recovered and had remained free of attacks. Evidence indicated that the paroxysms of hypertension are due to intermittent hypersecretion of epinephrine into the blood stream by the chromaffin tumor of the adrenal gland.

CAUSE OF DEATH RESULTING FROM MASSIVE INFUSIONS OF ISOTONIC SOLUTIONS .

AN EXPERIMENTAL STUDY

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The therapeutic status of intravenous infusion has undergone an important revision in the last few years. Just as the discovery of blood groups and their interrelations early in the present century made possible the extensive use of blood transfusions, so, more recently, has the discovery of the so-called "pyrogenic factor" in the causation of "infusion reactions" and of methods for its elimination made feasible the extensive use of intravenous infusions.

Prior to about ten years ago it was commonly held by well informed practicing physicians that intravenous injections were essentially dangerous because they always involved the risk of disrupting such compensatory mechanisms as those which maintain the acid-base balance, the osmotic tension and the viscosity of the blood. These mechanisms were conceived to be delicately balanced and easily upset. Accordingly, solutions for intravenous use were carefully compounded from "triple-distilled water" and if they were to be given in any considerable quantity were also carefully "buffered."

Physiologists had long known that experimental animals survive infusions of physiologic solution of sodium chloride, even though the solution is prepared without benefit of complicated physicochemical theories, in volumes far exceeding any ever used clinically;[1] but when using these solutions clinicians encountered "infusion reactions" in man which are not recognized, or at least are encountered only in very mild forms, in the lower animals. In spite of the fact that the outstanding clinical features of such reactions were chills and fever, almost every conceivable theory of their causation was entertained except the obvious

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1. Dastre, A., and Loye, P.: Le lavage du sang, Arch. de physiol. norm. et path. 2:93-114, 1888.

one that something in certain solutions, not present in others, affected the temperature-regulating mechanism of the body. Man, possessing a more unstable temperature-regulating mechanism than other animals, would naturally be particularly susceptible to the effects of such an entity.

Not until the painstaking experimental investigations of Rademaker,[2] based on preceding observations by Seibert,[3] were published did the real source of the "infusion reaction" come to be appreciated. As a result of these investigations and others substantiating them [4] has come the installation of "solutions laboratories" in the larger hospitals. In these laboratories scrupulous care is exercised in the preparation of solutions and apparatus so that they are free from reaction-producing contaminations. Another result is the commercial production by medical supply houses of complete infusion outfits containing any of the solutions at present considered useful, together with the necessary rubber tubing and needles. These are prepared in convenient sterile packages, ready for immediate use and conforming with the highest laboratory standards.

Such developments in technic have reduced the incidence of infusion reactions so near to the vanishing point that hypodermoclysis and proctoclysis are rapidly becoming obsolete in many institutions. It has recently been felt by many physicians that this release from what amounted to a superstition, accomplished without introducing into the solutions themselves any substance except the chemically pure dextrose, sodium chloride or other simple chemical compounds and the distilled water in which they are dissolved, opens the way to new dangers which are likely to be engendered by undue confidence.[5] Because of the natural tendency to overdo any form of therapy which is relatively free from immediate danger, it seems that the time is now ripe for a more extensive laboratory appraisal than has yet been made of the basic responses to massive infusions. To assume that such simple solutions of dextrose and sodium chloride as are commonly used as vehicles are assimilated and utilized in precisely the same manner as they would be if they were absorbed from the intestinal tract and that

2. Rademaker, L.: The Cause and Elimination of Reactions After Intravenous Infusions, Ann. Surg. **92**:195-201, 1930; Reactions After Intravenous Infusions: A Further Study on Their Elimination, Surg., Gynec. & Obst. **56**:956-958, 1933.

3. Seibert, F. B.: Fever-Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67**:90-104, 1923.

4. Co Tui; McCloskey, K. L.; Schrift, M., and Yates, A. L.: A New Method of Preparing Infusion Fluids Based on the Removal of Pyrogen by Filtration, J. A. M. A. **109**:250-252 (July 24) 1937.

5. (a) de Takáts, G.: Push Fluids: Surgeons' Postoperative Order, Am. J. Surg. **11**:39-44, 1931. (b) Fantus, B.: Fluid Postoperatively: A Statistical Study, J. A. M. A. **107**:14-17 (July 4) 1936.

the reactions of the circulation to the effects of bulk or volume can be predicted or explained on the basis of what is already known of hemodynamics, until checked by laboratory data, is distinctly gratuitous.

In our laboratory we have been performing certain simple but fundamental experiments designed to test the intermediate and ultimate fate of the simpler solutions, particularly of sodium chloride and dextrose, which are so commonly used clinically in considerable volumes for intravenous infusion.

In a previous report [6] we described some of the physiologic responses of the cat to massive infusions of 1 per cent sodium chloride solution. In the present communication we have to report some observations on the infusion of 5 per cent dextrose solution. These observations, in conjunction with previously reported and as yet unreported additional data on sodium chloride solution, seem to present a virtually complete picture of the cause of death when isotonic solutions of these two substances are injected at excessive rates and in excessive amounts.

METHOD

As in the previous series of studies, cats were used as experimental animals. The solutions were injected by gravity from an arsphenamine buret, which was ordinarily raised to such a level that the height of the column of fluid above the cannula varied from about 25 inches (63 cm.) when the tube was full to about 16 inches (40.5 cm.) when the level of the fluid had dropped to the last graduation. Additionally, however, we have on a number of occasions used a gravity system in which the height of the fluid reservoir above the animal was about 6 feet (182.8 cm.) and with which the rate of flow was adjusted to a constant volume output by a screw clamp and a glass dropping tube without any vent; this was in an attempt to stabilize the rate of delivery of fluid against minute variations by increasing the head of pressure. This modification of technic was found to offer no particular advantages over the original method, but as a check it is perhaps of some importance. Solutions were injected at approximately body temperature in all instances. Some experiments have been performed in which the temperature was accurately controlled by an electric heating device and thermometer placed just proximal to the cannula inserted into the vein of the animal. This refinement of technic, however, was found to be of little importance except as a check on the ordinary procedure of preheating the solution to a temperature sufficiently higher than that of the body to allow for the unavoidable loss of heat as the solution flows through the delivery system.

RATE AND VOLUME RELATIONS OF LETHAL DOSES OF ESSENTIALLY ISOTONIC SOLUTIONS OF SODIUM CHLORIDE AND DEXTROSE

In tables 1 and 2 are recorded representative data from experiments designed to determine the maximal rates at which prolonged infusions

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6. Cutting, R. A.; Lands, A. M., and Larson, P. S.: Distribution and Excretion of Water and Chlorides After Massive Saline Infusions: An Experimental Study, Arch. Surg. **36**:586-613 (April) 1938.

can be given and the total amounts which can be infused before death
supervenes. Only observations obtained under the most carefully con-
trolled conditions have been included in the tables. Although the num-
ber of cases shown in table 1 is less than the number shown in table 2,
the average value is probably as reliable in the one instance as in the

TABLE 1.—*Lethal Doses of 1 Per Cent Sodium Chloride Solution*

Animal Number	Weight in Kilograms	Rate of Infusion, Cc./Kg./Min.	Total Amount Infused, Cc./Kg.	Retained Fluid, Cc./Kg.	
				Including Peritoneal Fluid	Not Including Peritoneal Fluid
S-35	2.10	3.7	679	575	468
S-36	1.70	5.6	727	495	423
S-37	1.90	5.8	606	522	450
S-38	1.70	4.8	742	519	446
S-39	1.75	5.7	777	666	540
Mean..........................		5.1	706.2	555.5	465.4
Mean variation................			7.2 per cent	9.4 per cent	6.7 per cent

TABLE 2.—*Lethal Doses of 5 Per Cent Dextrose Solution*

Animal Number	Weight in Kilograms	Rate of Infusion, Cc./Kg./Min.	Total Amount Infused, Cc./Kg.	Retained Fluid, Cc./Kg.	
				Including Peritoneal Fluid	Not Including Peritoneal Fluid
S-13	2.57	3.8	535	352	294
S-14	2.15	4.1	405	358	299
S-16	2.35	3.5	511	345	286
S-17	2.15	3.9	368	300	280
S-18	2.30	3.3	391	370	319
S-19	2.60	4.0	433	291	253
S-22	2.45	4.2	531	409	384
S-25	2.80	4.5	516	339	296
S-26	2.10	4.8	350	309	283
S-27	2.40	4.6	406	358	322
S-31	1.95	4.8	559	328	274
S-32	2.05	4.5	450	387	328
S-33	2.00	4.8	393	320	279
S-40	2.60	4.6	574	344	311
S-41	2.37	4.0	557	376	339
Mean..........................		4.2	465.3	345.7	303.2
Mean variation................			15.1 per cent	7.33 per cent	8.05 per cent

other, for in both instances the averages have been checked against
considerably larger series of not quite so well controlled experiments.

In explanation of the recorded values, it should be emphasized that
the rates called "maximal" refer to prolonged injections, not to speeds of
injection which are initially tolerated or which can be maintained at
odd intervals for short periods. It should be obvious that compensatory
mechanisms which may be adequate during the first minutes of a massive
infusion may fail as the cumulative strain of infusion during many

minutes becomes felt, or that repeated surges of strain of short duration may fail to break down compensatory mechanisms which would succumb under continuous pressure of similar magnitude.

As will immediately be seen, it is possible to give 1 per cent saline solution considerably more rapidly and in considerably larger total amounts than 5 per cent dextrose solution. With cats, it is possible to infuse 1 per cent saline solution at rates averaging 5.1 cc. per kilogram of body weight per minute, whereas for 5 per cent dextrose solution the maximal rate of infusion averages only 4.2 cc. per kilogram per minute. Cats tolerate saline solution in total amounts up to 706 cc., whereas they tolerate dextrose solution in total amounts up to only 465 cc. per kilogram of body weight.

All the infusions represented in these two tables were carried to the actual death of the animals. The volumes of retained fluid, tabulated in the last two columns, were calculated by subtracting from the total volume of fluid infused the volume of urine which, during the infusion, drained away through a retention catheter introduced into the bladder. The mathematical difference between the figures in the last two columns for each animal represents the amount of peritoneal fluid collected from the abdominal cavity directly after death. As might reasonably be expected, the amount of retained fluid for animals given lethal doses of saline solution was considerably greater than that for animals to which the dextrose solution had been administered (in the ratio of 555 to 345 cc. per kilogram of body weight, including peritoneal fluid).

With only such values before one, it might seem logical to conclude that because the rate and volume tolerated in the case of saline solutions are so definitely greater than the rate and volume in the case of dextrose solutions, the chemical composition of the infused fluid must be the important factor in causing death. As a matter of fact, a study of the changes in blood pressure associated with massive infusions seems to indicate otherwise, at least as far as the immediate cause of death is concerned.

BLOOD PRESSURE CHANGES RESULTING FROM MASSIVE INFUSIONS

Chart 1 is a kymographic record of respiratory and arterial blood pressure responses to a lethal infusion of 5 per cent dextrose solution. In every essential respect, the tracing, which is representative for dextrose solutions, conforms to tracings obtained during infusions of 1 per cent saline solutions.[6] The respiratory portion of the kymogram shows nothing of particular importance except for a period of hyperpnea associated with vomiting, which the animal showed relatively early in the infusion, and a gradual progressive increase in the amplitude of respirations as more and more of the solution accumulated in the body

of the animal, especially (toward the end of the infusion) in the abdominal cavity; as the animal became overwhelmed, the amplitude of the respirations again diminished to the point of final apnea.

The tracing of the arterial pressure shows in the first fifteen minutes a slight increase in mean systolic pressure; this, however, did not exceed 10 mm. of mercury. With the attack of vomiting the pressure decreased in typical fashion. As the animal became overwhelmed by the infusion the pulse pressure increased progressively, whereas the mean arterial blood pressure decreased to the terminal stages of failure of the
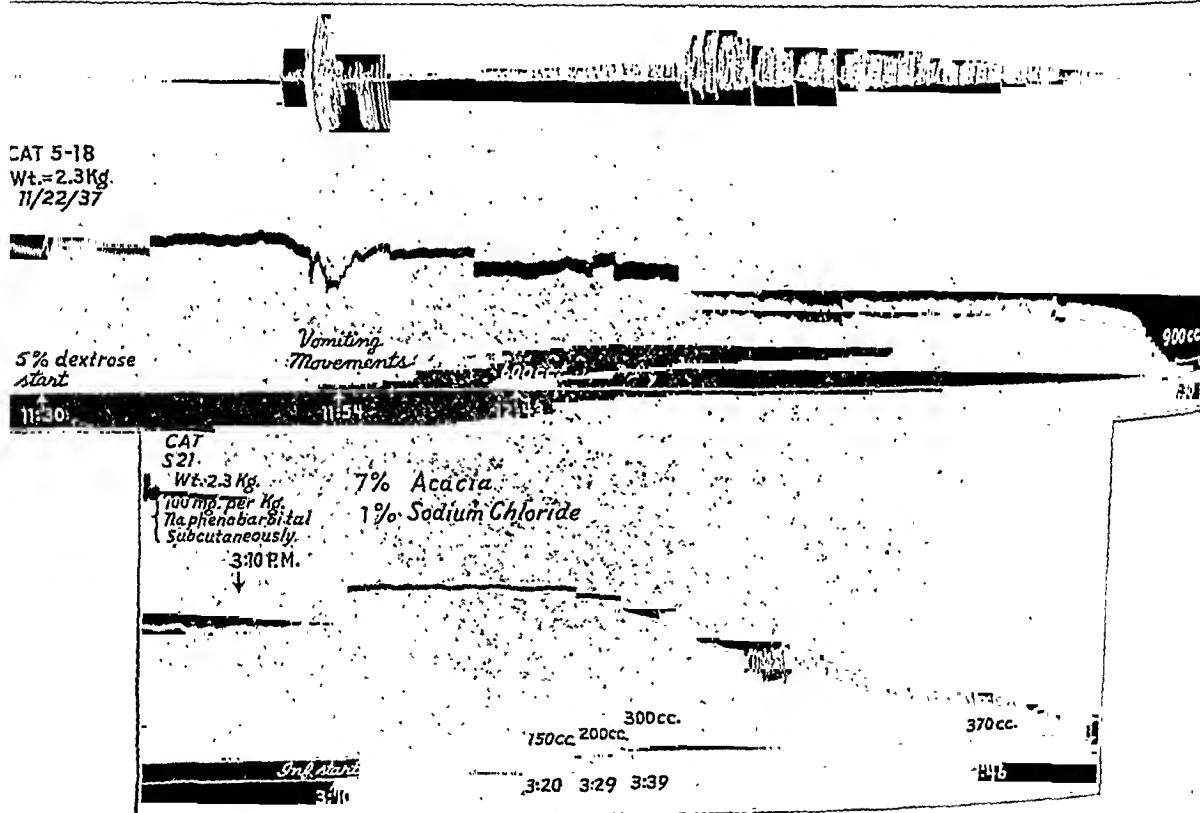
Chart 1.—The upper portion of the chart represents the response of the blood pressure of the cat to a lethal infusion of 5 per cent dextrose solution. The lower portion represents the response of the blood pressure to a lethal infusion of "gum-saline" solution (7 per cent acacia in 1 per cent solution of sodium chloride).

circulation. Though the condition is not well shown in this particular tracing, the last few minutes of infusion was characteristically associated with bradycardia.

The kymogram at the bottom of the figure represents a typical response of the arterial blood pressure to a lethal infusion of 7 per cent acacia in 1 per cent sodium chloride solution, the familiar "gum-saline" solution used clinically. Both the upper tracing and the lower one have been considerably telescoped for purposes of reproduction, but not in

exactly the same proportion; the lower tracing, in order to be strictly comparable, should have been shortened to only a little more than one-third the length of the upper one. It takes approximately two and one-half times as much 5 per cent dextrose solution as gum-saline solution to cause death when the two are given at comparable rates, and, accordingly, an animal given 5 per cent dextrose solution survived almost three times as long as one given gum-saline solution. Except for this, however, the changes in the arterial blood pressure are similar; the early increase in mean arterial pressure is in evidence, amounting in this instance to about 36 mm. of mercury, and as the animal becomes over-whelmed by the solution the progressive decrease in mean arterial pressure, the increase in pulse pressure and the terminal bradycardia are all well shown.

The suggestion is obvious that all three solutions, physiologic sodium chloride, physiologic dextrose and physiologic acacia, when infused in massive amounts cause death by overloading the circulation. Further evidence of this is afforded by a study of responses of the circulating blood volume and by estimations of venous pressure.

EFFECT OF MASSIVE INFUSIONS ON CIRCULATING BLOOD VOLUME AND VENOUS PRESSURE

It seems highly improbable that any method now in use for the esti-mation of true blood volume, plasma volume or red cell volume is capable of close or accurate interpretation. This is, without doubt, par-ticularly true under conditions which tend to change blood volume pro-foundly, such as severe hemorrhage or massive infusion. The reason seems to lie in the impossibility of differentiating between vascular changes due to gain or loss of fluid and those due to vasomotor or circulatory changes.[7] No special comment need be made on the well recognized fact that under changing conditions the total bulk of the blood within the entire vascular tree is capable of relatively rapid gains or losses by virtue of the passage of water and certain other substances in solution from the terminal ramification of the vessels to the extra-vascular tissue spaces and vice versa. The effect of vasomotor or cir-culatory changes is not quite so obvious. There is some evidence that at least two important mechanisms may be operative. One of these leads to the stagnation of concentrated blood in certain areas of the body. Krogh, cited by Hooper and his associates,[8] illustrated this par-

7. Lampson, P. D., and Rosenthal, S. M.: Inadequacy of Our Present Blood Volume Methods, Am. J. Physiol. 63:358-367, 1923.

8. Hooper, C. W.; Smith, H. P.; Belt, A. E., and Whipple, G. H.: Blood Volume Studies: Experimental Control of a Dye Blood Volume Method, Am. J. Physiol. 51:205-220, 1920.

ticular mechanism in his description of the physiologic effect of applying a small drop of ethyl carbamate (urethane) solution to a single narrow capillary and arteriole in the mucous membrane of the frog's tongue:

While the arteriole remains narrow, the capillary dilates more and more as the blood flows into it and little or no blood flows out from the venous end, but at the same time, the concentration of the blood is visibly increased from moment to moment. The corpuscles become packed together, forming a solid clump near the venous end; this clump grows into a long column by fresh corpuscles being added to it. One is able to watch quite distinctly how the plasma disappears from the normal blood entering the capillary, while the corpuscles are piled up until, finally, the whole strongly dilated capillary is completely filled and we have the typical stasis. The entire plasma, with all its colloids, is filtered off through the capillary wall. . . . A number of other observations and experiments show that the increased permeability cannot be due to any specific action of the ethyl carbamate but is a regular accompaniment of dilatation quite irrespective of the manner in which the dilatation is brought about.[9]

The other mechanism seems to provide for local dilution of the blood in certain areas and thus is the antithesis of the mechanism just described. Illustrative of the evidence for its existence is the following: Miller and Poindexter [10] found no demonstrable increase in circulating blood volume, as measured by the dye method, following rapid intravenous administration of rather large quantities of 0.9 per cent sodium chloride solution; hematocrit readings, on the other hand, indicated an average dilution of about 20 per cent. Crandall and Roberts [11] found the same discrepancy between the two methods of determining circulating volume following injections of 5 per cent dextrose solutions. They attempted to explain this on the basis of the hypothesis that the added fluid dilutes the blood in certain vessels, particularly those in the splanchnic area, to a greater extent than is the case elsewhere in the body, for they found that if they infused 50 to 100 cc. per kilogram of body weight of isotonic dextrose or saline solution into dogs with Eck fistulas, estimations of the blood volume by the dye method showed a definite increase in 4 out of 5 animals, accounting for as much as 40 to 50 per cent of the injected fluid.

Meek and Eyster [12] have shown, by means of photomicrographs of the capillaries and venules of the ear of the dog after intravenous

9. Krogh, A.: The Anatomy and Physiology of Capillaries, New Haven, Yale University Press, 1923.

10. Miller, J. R., and Poindexter, C. A.: The Effects Observed Following the Intravenous and Subcutaneous Administration of Fluid: An Experimental Study on Dogs, J. Lab. & Clin. Med. 18:287-297, 1932.

11. Crandall, L. A., Jr., and Roberts, G. M.: Blood Volume After Intravenous Fluid in Normal and Eck Fistula Dogs, Am. J. Physiol. 101:24-25, 1932.

12. Meek, W. J., and Eyster, J. A. E.: Reactions to Hemorrhage, Am. J. Physiol. 56:1-15, 1921.

injection of acacia-saline solution, that these vessels act as reservoirs preventing any increase in the volume of the effective circulation. Thaysen [13] stated that if the erythrocytes were counted systematically over long periods in cases of polycythemia, remarkable fluctuations in the count would probably be found. He reported a case in which the erythrocyte count ran in the course of twelve hours from 5,300,000 to 10,600,000. His investigations and tests showed that the fluctuations were caused by varying contraction and dilatation of the capillaries and precapillaries of the skin.

Hooker [14] summarized the situation as follows:

If the body has at its control such a highly organized device for the disposition and partition of the blood by which extensive capillary beds may be largely emptied of or packed with corpuscular elements or plasma, an explanation is readily found for the uncertainties of blood cell counts and blood volume determinations. Individual capillaries may be opened up or closed or they may be gorged with stagnant inactive corpuscles, as is possible to demonstrate on the finger. Mediation of these and similar changes would be accomplished by activation of the arteriole, capillary or venule functioning individually or collectively. It is natural to infer that normally such forces are well balanced and counteract one another so that the volume and corpuscular composition of the blood is held relatively stable, but in time of physiological stress or in disease the alterations which develop might assume considerable proportions.

Our experiments confirm the observation of others that although repeated estimations of the hemoglobin content during the course of a massive infusion seem to indicate that the circulating blood is undergoing considerable dilution, estimations of the blood volume according to "dye methods" give evidence that the increase in volume may be only moderate. Thus, in a typical experiment, assuming the normal circulating blood volume of the cat to be 63 cc. per kilogram of body weight (actual average for 11 animals), we found that after infusion of 200 cc. of 1 per cent saline solution per kilogram of body weight, the circulating volume as determined by the dye method was 78.7 cc. per kilogram, whereas hemoglobin dilution indicated a circulating volume of 104 cc. per kilogram.

With the reservations implied in the foregoing discussion of the value of hemoglobin dilution as a measure of circulating blood volume, the following data are presented:

Chart 2 shows simultaneous comparisons of "blood volume" estimated by the hemoglobin dilution method and estimations of venous pressure in animals given lethal infusions of 1 per cent saline solutions. and chart 3 shows similar comparisons for animals given lethal infusions of 5 per cent dextrose solutions.

13. Thaysen, T. E. H.: Polycythemia, abstracted, J. A. M. A. **75**:72 (July 3) 1920.

14. Hooker, D. R.: The Functional Activity of the Capillaries and Venules, Am. J. Physiol. **54**:30-53, 1920.

The upper portion of each figure is a graph in which a large number of estimations of blood dilution have been plotted on the basis of changes in hemoglobin concentration of the blood. The hemoglobin dilution is plotted vertically, and the volume of infused solution per kilogram of body weight of the animal is plotted horizontally; the horizontal ordinate can, of course, be used as an approximate measure of the duration of infusion, inasmuch as rates of infusion were comparable in all cases.
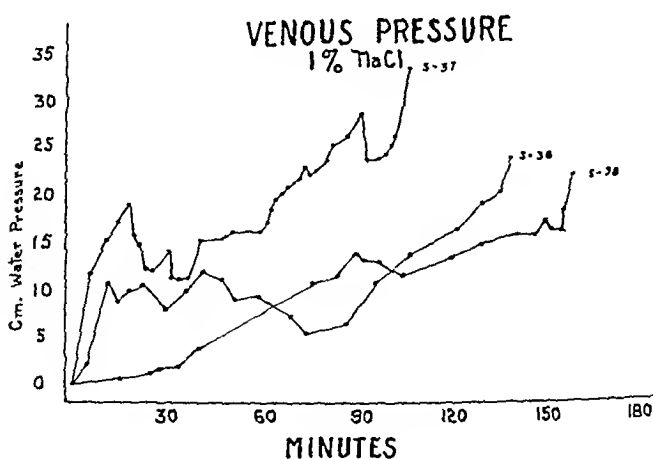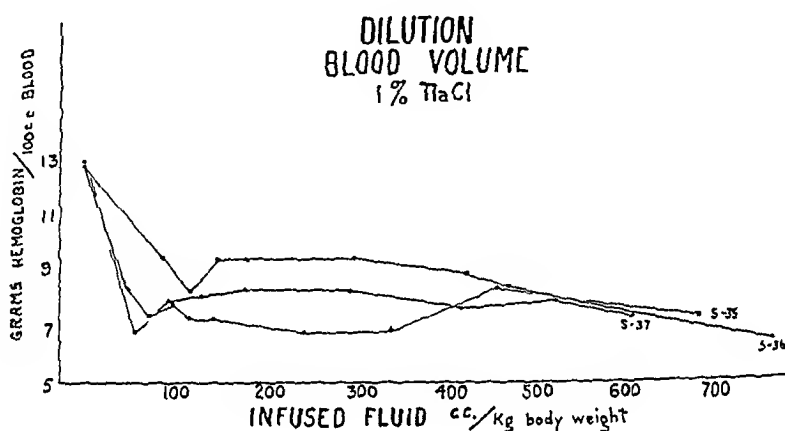
Chart 2.—The upper curve is a graph showing dilution of hemoglobin. For reasons explained in the text the hemoglobin dilution may not be taken as a direct measure of the magnitude of changes in the blood volume, but the conclusion seems unavoidable that some increase in circulating blood volume does occur as a large infusion progresses, as suggested by this curve, and explains at least in part the increase in venous pressure which is graphically shown in the lower curve. Such a view is certainly in accord with the observation of Meek and Eyster [16] that increase in stroke volume and increase in diastolic size of the heart results from intravenous infusions and our own observation (fig. 1) that increased pulse pressure without bradycardia (except terminally) occurs.

The lower graph in each of the two figures represents venous pressure in centimeters of water, as measured by a simple single-armed water manometer filled with physiologic solution of sodium chloride and connected by a short piece of rubber tubing to a cannula introduced into one of the external jugular veins of the animal. The error introduced by treating the pressure of the saline solution as pure water pressure is negligible.
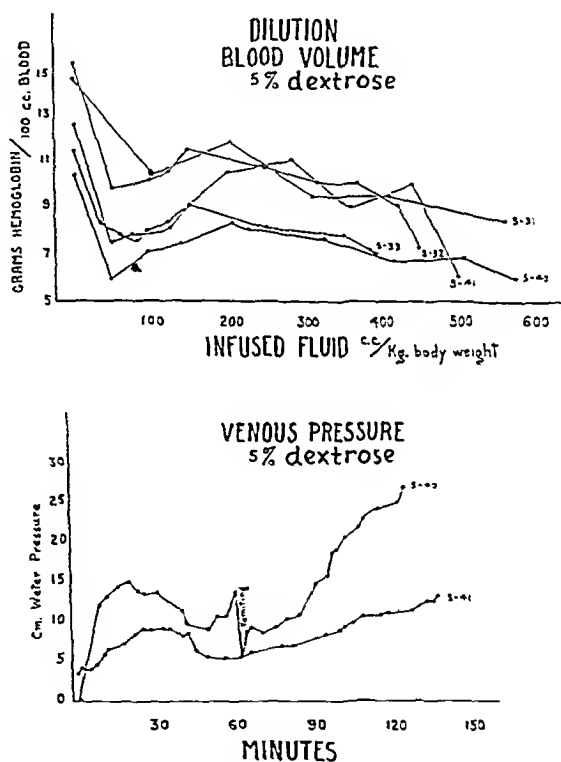
Chart 3.—The treatment and interpretation are the same as for figure 2. Dextrose instead of saline solution was used.

The most important feature of the venous pressure curves is the progressive increase as more and more fluid is infused. In most cases more than a third of the entire increase in venous pressure occurs within the first fifteen minutes of the infusion period; in other words, the curves commence with an abrupt rise.

The obvious explanation for this is that the added fluid increases the bulk of the circulating blood. and the venous blood pressure therefore rises.

Following the initial period characterized by an increase in the venous pressure there occurs a phase of reversal which we are rather at a loss to explain. During the ensuing period of approximately thirty minutes, i. e., in the interval from fifteen to forty-five minutes, the hemoglobin concentration increases slightly, while the venous pressure declines slightly. Inasmuch as during this period the infusion was continued at the same regular rate as before, the explanation must obviously be sought either in an unusually rapid diffusion of water out of the vascular system (such that diffusion actually occurred faster than fluid was added to the circulation) or in some relative addition to the circulation of hemoglobin in the form of red blood cells, such as might occur as a result of contraction of the spleen. Of the two possible explanations the former seems the more probable, especially in view of the fact that the phenomenon occupies a considerable period, during which additional water is being rapidly poured into the circulation. Although we have no evidence to indicate that such is the case, it is possible that during this period some special storage reservoir of the body, such as the peritoneal cavity, is rapidly opened. Perhaps, on the other hand, the mechanical dilation of the smaller blood vessels is associated at a certain point with a sudden marked increase in permeability the effect of which dominates the picture for a time.

At all events, whatever this intermediate mechanism may be, it ultimately fails to provide the necessary differential, and thereafter the hemoglobin concentration progressively declines while the venous pressure progressively increases until death supervenes.

It thus appears that increasing venous pressure is the immediate cause of death. Wiggers and Katz [15] and Meek and Eyster [16] have shown that in "good hearts" a circulatory crisis of decompensation occurs when the pressure of blood in the atrium reaches 250 to 310 mm. of water. The venous pressure just before death for 2 of our 5 animals definitely fell within this range, and values for 2 of the remaining 3 at death rather closely approached it. In 1 of the 5 animals, on the other hand, the venous pressure at death was considerably less. It may be that this discrepancy was due to the fact that this animal did not have a "good heart" to begin with. At all events, Wiggers' experiments and ours are not exactly comparable. Apparently, increases in venous pressure were produced very rapidly in Wiggers' experiments, even though they were produced by infusions of saline solution, whereas in our experiments the increase in venous pressure was gradually built up

15. Wiggers, C. J., and Katz, L. N.: The Contour of the Ventricular Volume Curves Under Different Conditions, Am. J. Physiol. **58**:439-475, 1922.

16. Meek, W. J., and Eyster, J. A. E.: The Effect of Plethora and Variation in Venous Pressure on Diastolic Size and Output of the Heart, Am. J. Physiol. **61**:187-202, 1922.

during more than two hours. Thus the duration of the exposure to increased venous pressure may have weakened the hearts of certain of our animals to such a degree that they actually succumbed to a relatively low intra-atrial pressure.

We have been interested in the question whether at the time when the circulating blood volume is at its maximum the vascular system is actually dilated to its utmost physiologic capacity. That this is probably not true is suggested by the results shown in chart 4. This is a kymogram showing the effect of allowing animals to inhale amyl nitrite at intervals throughout a massive infusion of 1 per cent sodium chloride solution. The depressions in the blood pressure that consistently result from this procedure suggest that the vasodilator mechanism is still
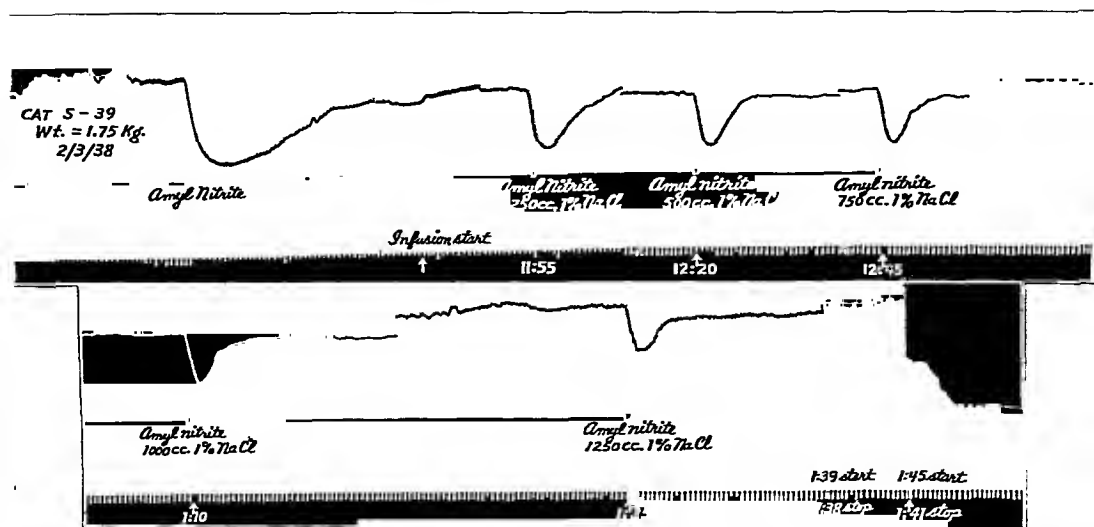
Chart 4.—Characteristic response to administration of amyl nitrite throughout a lethal infusion of 1 per cent saline solution.

active even up to about four minutes before death in an infusion which lasts nearly two hours. The drug, being in gaseous form, could not conveniently be given in measured doses, and for this reason the responses cannot be considered as quantitatively comparable. The fact, however, that all of the inhalations during the actual infusion showed responses of approximately the same magnitude somewhat suggests that vasodilator mechanisms play no more than a minor role in the accommodation of the circulatory system to increased volumes or, from another point of view, may be taken as evidence that there is little actual increase of blood volume to be accommodated.

Considering the evidence afforded by arterial pressure, venous pressure and blood volume and the apparent similarities of response evoked

by saline, dextrose and acacia infusions, we believe there can be little doubt that the cause of death induced by massive infusions of isotonic solutions of these substances is the same in all cases. The animals die as a result of circulatory failure. Terminally the respiratory center fails first, and directly thereafter the heart undergoes complete decompensation, with the values for blood volume and venous pressure at the maximum.

GROSS OBSERVATIONS AT AUTOPSY

In general, the gross observations at autopsy on a cat dying from massive infusions of 5 per cent dextrose solution are closely similar to those shown by an animal dying from a massive infusion of 1 per cent saline solution. The following is a typical protocol recording all the features usually noted in the case of dextrose solutions.

External Examination.—There is distention of the abdomen, but little edema either of the extremities or of the body wall. No other features of interest are seen.

Peritoneal Cavity.—When the peritoneal cavity is opened it is seen to be filled with clear serous fluid, which measures 70 cc. The stomach and intestine are both moderately edematous. The former contains 15 cc. of clear yellow bile-stained fluid. The latter contains 35 cc. of clear nonmucoid, nonbile-stained fluid. The large intestine presents a normal appearance externally and on being incised is found to contain a moderate amount of formed feces covered with mucus. The liver is perhaps slightly enlarged but is otherwise normal in color and general appearance. The gallbladder is pale, contracted and virtually empty. The pancreas, the retroperitoneal space and the adjacent spaces between the leaves of the mesentery present a remarkable appearance; a gelatinous edema pervades this area and has widely permeated the pancreas, so that the latter appears broken up into a series of lobulations, the fragmented organ being very pale.

The kidneys are somewhat enlarged and pale; their capsules are under tension, and when incision is made a small amount of clear serous fluid is discharged through the incision. The cut surface of these organs is pale and drips clear, colorless fluid. The spleen is normal in size and appearance.

Thoracic Cavity.—The pleural cavities together contain 10 cc. of clear serous fluid. The surfaces of the lungs are spotted diffusely with minute petechial hemorrhages. The upper lobes are pink, crepitant and apparently normal. The lower lobes are congested, dark bluish red and definitely edematous; clear, frothy fluid can be squeezed from their cut surfaces. The chambers of the heart are collapsed, but otherwise the organ is normal in appearance; the pericardium contains no extraordinary amount of fluid.

Cranial Cavity.—The cerebrum appears normal; the convolutions are well marked, and there are no evidences of either compression or shrinkage of the organ. Only a normal amount of cerebrospinal fluid is found.

As has been stated, the variations from normal seen in these animals are similar in many respects to those seen in animals succumbing to the effects of massive infusions of saline solution. The pancreatic and retroperitoneal gelatinous edema, which is the most remarkable anatomic feature at autopsy in both cases, is, however, definitely less spectacular after dextrose infusions. In both cases there

is considerable free colorless watery fluid in the peritoneal cavity—less after dextrose infusions, as might be expected. Pulmonary edema, present in both cases, is less marked after dextrose infusions. Gross evidence of cerebral edema is seen in neither, but most of the other tissues are pale and watery under both conditions. The characteristic differences are: (1) Buccal and nasal secretions are more copious in the case of saline infusions; (2) animals receiving such infusions show diarrhea, which is absent in the case of dextrose infusions (colonic contents are formed and almost normally inspissated); (3) the gallbladder is distended and full after saline infusions, contracted and empty after dextrose infusions; and (4) the heart is full and dilated in the former case, empty and flabby in the latter. We have not observed in these experiments in which death was more or less suddenly produced the gross lesions described by Jacobs and Colwell [17] which apparently are seen after ·prolonged dextrose injections in dogs, namely, congestion of the serous membranes and meninges, hyperemia, swelling and softening of the hypophysis, pallor, enlargement and friability of the liver, congestion, gross hemorrhage and even frank gangrene of the pancreas.

The changes which we have observed apparently are not inconsistent with complete and relatively rapid return to normal, for if the infusion is stopped somewhat short of actual failure of the heart, some animals make an uneventful recovery within from twenty-four to thirty-six hours. If such animals are killed and autopsy is performed after five or six hours, most of the gross abnormalities are found to have abated. Except for the presence of some clear peritoneal fluid and a condition of the retroperitoneal tissues and the pancreas which is approximately midway between the intense edematous condition found at the end of the infusion and the normal appearance of these parts, there is little evidence of abnormality within the abdominal cavity. Within the thorax the pathologic changes of the lungs have entirely disappeared except at the extreme bases, and the heart appears normal.

At the end of about twenty-four hours the gross appearance of the contents of the abdominal and thoracic cavities may be normal.

INTRINSIC TOXICITY OF DEXTROSE

Although we believe that the foregoing is an accurate description of the cause of sudden death resulting from infusions of isotonic solutions of either dextrose or sodium chloride at rapid rates, we have reason· for believing that if such infusions are interrupted just short of death the subsequent course of events may not be exactly the same with both solutions. Animals given infusions of just sublethal doses of saline

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17. Jacobs, H. R., and Colwell. A. R.: Lesions in the Pancreas and in the Anterior Hypophysis with Fatal Acidosis Following Prolonged Intravenous Administration of Glucose (in Dogs), Am. J. Physiol. **116**:194-200, 1936.

solution recover without exception, and, as far as clinical indications go, their recovery is virtually complete within twenty-four hours. Such animals live indefinitely and show no complications or sequelae as far as can be clinically observed. Animals given infusions of just sublethal doses of dextrose solution, on the other hand, are quite as likely to die within a few hours as to live, and if they live they are likely to remain drowsy and depressed for a period varying from twenty-four to forty-eight hours. The depressed animals sometimes present peculiar clinical manifestations ranging all the way from a sort of general stupidity to muscular twitchings; the latter amount at times to mild tonic and clonic convulsions. In a single instance the animal's behavior was that characteristically seen after decerebration. In this case there were blindness, general muscular weakness (affecting particularly the hindlegs, though not to the extent of preventing the animal from standing) and a definite tendency to develop cataleptic postures, which were maintained for minutes at a time. Animals showing moderate depression usually recover and ultimately live indefinitely in an entirely normal condition. Those showing severe degrees of toxicity die after variable intervals.

Such convalescent peculiarities of animals infused with massive doses of 5 per cent dextrose solutions, which are never seen in animals infused with 1 per cent saline solutions, suggest that dextrose in the concentrations in which it occurs terminally as a result of such infusions is itself toxic. The terminal blood sugar levels of the animals with which we carried the infusion to actual death were determined and found to range generally above 2,000 mg. per hundred cubic centimeters of blood, the actual range for 6 animals being from 1,980 to 2,620 mg. On the other hand, in the case of survival experiments, because of the impossibility of predicting the exact moment at which death will occur it is necessary to estimate on the basis of clinical manifestations when the lethal point is approaching and stop the infusion just in advance of it. In such cases, of course, one does not have the guidance of blood pressure tracings, and the tendency is naturally to err in the direction of conservatism. As a matter of fact, estimations of the blood sugar at the point of cessation of infusion in our survival experiments show that 2,000 mg. per hundred cubic centimeters of blood has never been exceeded. From the research which has appeared to date on the subject of dextrose metabolism under conditions of artificial addition of dextrose to the circulation, it appears that dogs do not survive blood sugar levels of more than 2,000 mg. per hundred cubic centimeters for much more than two hours, for at this level disturbances of renal function appear, and toxic manifestations are shown by unanesthetized animals.[18]

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18. Wierzuchowski, M.: Overflow Diabetes and Toxic Phenomena Due to the Infusion of Glucose in Normal Dogs. J. Physiol. **87:**85P-86P, 1936.

CONCLUSIONS

Animals tolerate intravenous infusion of isotonic solutions of sodium chloride or dextrose in much larger quantities and at much higher rates of speed than seems to be generally appreciated. If animals (cats) are not allowed to fall victim to either of the two common varieties of accidental death, aspiration drowning following regurgitation or fatal intoxication with fever-producing contaminants of water, infusions of isotonic sodium chloride can usually be given at rates as high as 5.1 cc. per kilogram of body weight per minute without causing death or interfering with complete clinical recovery and indefinitely continued health. Isotonic dextrose solutions may be equally well tolerated at a somewhat decreased speed of injection and in a somewhat smaller total amount, but still in relatively huge doses, that is, at rates up to 4.2 cc. per kilogram of body weight per minute and in volumes up to 465 cc. per kilogram of body weight per minute.

When such total doses or rates of infusion are exceeded, death occurs from cardiac decompensation. The physiologic mechanisms of blood dilution, capillary filtration into the tissue spaces, urinary excretion and secretion into the peritoneal cavity and gastrointestinal tract act as efficient compensating mechanisms up to a certain point. Beyond this, however, the vascular load gradually produces a progressively increasing venous pressure which, when it attains a value somewhere between 150 and 250 mm. of water in the great veins draining into the right side of the heart causes acute cardiac decompensation and death. The respiratory center undergoes paralysis due to anoxia a few minutes before the terminal abrupt fall in blood pressure which signalizes cardiac failure.

Gross pathologic observations on animals dying suddenly from the effects of such massive infusions fail to show evidence of cerebral edema. Pulmonary edema, especially at the bases of the lungs, ranges from moderate to severe. The peritoneal cavity contains relatively large collections of clear serous fluid, though the pleural and pericardial cavities contain little secretion. Secretion into the gastrointestinal tract is voluminous in the case of saline solutions and relatively slight in the case of dextrose solutions. The retroperitoneal space and the pancreas show a gelatinous edema which is the most spectacular feature of the pathologic picture. None of these changes is inconsistent with complete clinical recovery of the animal and an indefinitely prolonged life thereafter: in about twenty-four hours all gross evidence of change has disappeared in animals which are allowed to survive.

Dextrose solutions infused at the concentration and at the rate reported produce a blood sugar level of some 2,000 mg. per hundred cubic centimeters. Apparently this level is a critical one, below which the

intrinsic toxicity of dextrose is not so likely to be acutely felt but above which specific lesions are rapidly produced which themselves are fatal. Because of the peculiarities of individual susceptibility there is probably about an equal chance that animals in which the blood sugar levels have been brought to such a value for short periods, though they may survive for a while, will die within a period varying from twelve to twenty-four hours. In the remaining animals, however, no change may occur which is inconsistent with complete clinical recovery. The failure of animals to tolerate as great a speed of injection or as large total quantities of dextrose as of saline solution for short periods is probably associated not so much with this phenomenon as with the fact that dextrose solutions do not undergo diffusion from the blood stream or elimination either by the kidney or the gastrointestinal tract with the same facility as do saline solutions.

OPERATIVE TREATMENT FOR BENIGN RECTAL STRICTURE (LYMPHOGRANULOMA VENEREUM)

PRELIMINARY REPORT

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It is generally conceded that the large majority of nonmalignant and nontraumatic strictures involving the rectum, especially those occurring in Negro women, are caused by lymphogranuloma venereum. Many articles have appeared in the medical literature describing this condition since Frei[1] introduced his intracutaneous test in 1925.

The causative agent is thought to be an ultramicroscopic virus transmitted during coitus, which after an incubation period of one week causes a transient, painless ulcerative lesion on the genitals. Two weeks later there is edema of the lymph nodes draining the initial lesion. associated with hyperplasia of the lymphoid tissues, fibrosis and abscess formation. These secondary manifestations vary with the sex of the patient and the location of the primary lesion. Martin and Bacon[2] in their detailed report of this condition stated:

There exists a dense network of lymphatics in the external genitalia and anorectal region of both the male and female. Those of the prepuce and frenulum pass to the superficial inguinal nodes, whereas those from the glans sulcus coronarius and mucosa of the urethra drain into the deep subinguinal nodes. . . . Thus, the superficial, inguinal and the superficial and deep subinguinal nodes form an unbroken chain, the afferents of which pass mainly to the external iliac nodes. There also exists a minor network . . . which anastomose with those of the prostate, bladder and ano-rectal glands of Gerota.

The lymphatics of the vulva and clitoris in the female are almost identical with those of the prepuce and glans in the male, since the network of the vulva drains for the most part into the superficial inguinal nodes, and those of the clitoris into the deep subinguinal nodes. There exist . . . two lymphatic plexuses in the vagina the collective vessels of which are arranged in three groups. The superior and middle groups drain the upper and middle thirds of the vagina and empty into the hypogastric glands and external iliac glands, whereas the inferior group

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1. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr. 4:2148-2149 (Nov.) 1925.

2. Martin, C. F., and Bacon, H. E.: Lymphogranuloma Inguinale or Lymphopathia Venerea, Internat. Clin. 4:250-293 (Dec.) 1935.

drains into the anorectal glands of Gerota, into those of the promontory of the sacrum and the hypogastric glands. Because the lymphatic network represents an almost unbroken chain, it is not difficult to understand the manner in which the anorectal glands of Gerota located between the rectal fascia and the longitudinal muscle layer of the rectum and the superior hemorrhoidal glands situated in the mesorectum, can receive lymph from these portions of the vagina as well as the lower portion of the cervix.

Excellent illustrations of the lymphatics involved in lymphogranuloma venereum may be found in a recent article by Lee and Staley.[3]

In the female the first evidences of rectal dysfunction are usually proctitis and superficial ulceration involving the lower two thirds of the rectum. Lymph stasis in the rectal wall below the involved nodes then develops, with edema and secondary infection. Months or even years may elapse before the typical dense but friable annular stricture appears. Fibrosis continues, with narrowing of the lumen until almost complete intestinal obstruction results.

Women appear more prone to systemic reaction than do men. Abdominal pain, weakness, irregular fever and pain in the joints often appear early. Nausea and vomiting occasionally occur. A marked secondary anemia is a rather constant late finding, and amyloid changes in the kidney are not infrequent. Several of my patients have shown a definite psychotic reaction.

The statement is frequently made that lymphogranuloma venereum is a relatively innocuous condition and that radical procedures are not justifiable in the average case. This is not true of the cases observed in the Hospital Division of the Medical College of Virginia. The patients are anemic and cachectic, and many have been semi-invalids for years. Those in whom the condition is of long standing have various degrees of cardiovascular-renal disease. They do not, as a rule, come to the hospital until the onset of obstructive symptoms. Secondary infection is always present, and perirectal abscess and rectal fistulas are frequent complications. While the lesion is usually located in the middle and the lower portion of the rectum, an occasional case is encountered in which the upper portion of the rectum and the sigmoid flexure and even that part of the small intestine which is contained in the pelvis are involved by direct extension. Extensive ulceration may be present in the rectum, and cases have been reported of spontaneous perforation followed by generalized peritonitis. Simple dilation of the stricture or excision of tissue for microscopic examination sometimes results in peritonitis and death. Practically every large series of cases has included fatalities

3. Lee, H., and Staley, R. W.: Inflammatory Strictures of the Rectum and Their Relation to Lymphogranuloma Inguinale, Ann. Surg. **100**:486-495 (Sept.) 1934.

from this cause. I recently observed a case in which death occurred four days after gentle dilation of a stricture and removal of tissue for biopsy.

This hazard is due to two factors. The friable tissues involved tear when incautious dilation is done, and even gentle manipulation may rupture an abscess in the diseased wall of the rectum. In the majority
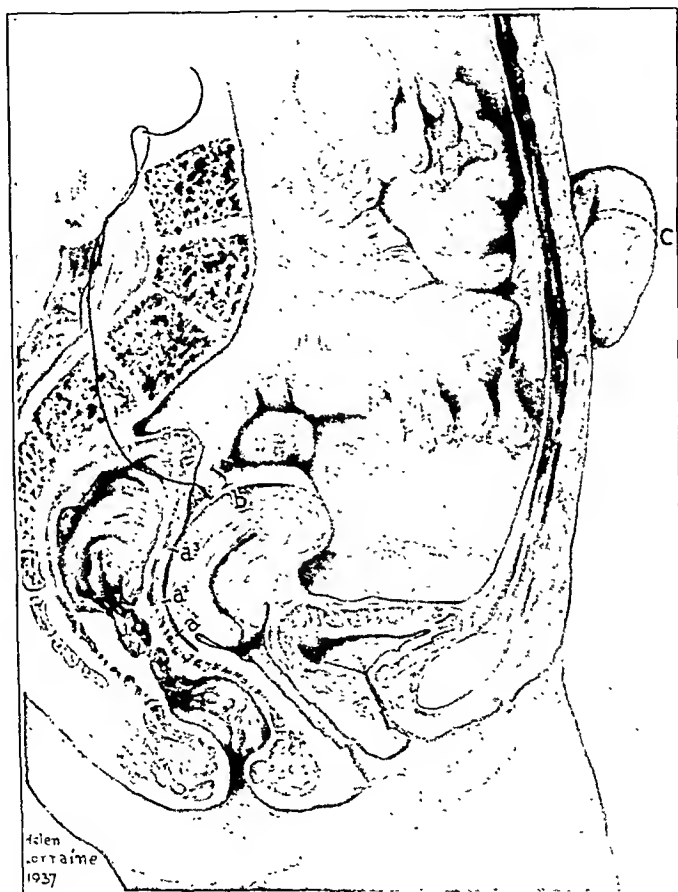
Method of obliterating the cul-de-sac and performing a "double-barreled" colostomy. The points marked a^1, a^2 and a^3 represent purse string sutures. (In recent operations only two pairs of purse string sutures have been used.) The point marked b denotes continuous suture which is used to close the defect between the posterior surface of the uterus and broad ligaments and the posterior parietal peritoneum and anterior surface of the sigmoid flexure. (In recent operations this suture has been placed at a lower level than is here depicted.) The point marked c denotes the point of division of the sigmoid flexure at the second stage of the operation.

of cases the stricture is located between 3 and 8 cm. above the muco-cutaneous border, and if the rectal wall is torn anteriorly the cul-de-sac of Douglas may be entered. In the female the rectouterine excavation is only 5.5 cm. from the anal orifice. Any stricture in the female that requires the introduction of the index finger past the second joint in order to palpate its upper limits is potentially dangerous.

In order that local procedures may be carried out without danger of peritonitis the following operation was devised and has been successfully performed on 10 patients with proved lymphogranuloma venereum during the past eighteen months. This procedure, in brief, is obliteration of the cul-de-sac by chemical irritation and suturing, followed by a colostomy. The operation suggests the Moschcowitz[4] procedure for rectal prolapse in that the true pelvis is closed in both cases. However, the purpose of the operation is entirely different, and the method followed is also dissimilar.

The technic is as follows: Spinal anesthesia is induced, and the patient is placed in the Trendelenburg position. A paramedian incision on the left is made from the symphysis pubis to the umbilicus. The distal portion of the colon and the pelvic contents are inspected. Diseased tubes and ovaries are removed. The intestines are packed away from the operative field, and the parietal peritoneum of the false pelvis is protected by moist sheets. The peritoneum lining the cul-de-sac is then painted with one-half strength tincture of iodine. Especial care is taken that the iodine comes in contact only with the area that will subsequently be covered by sutures.

A series of purse string sutures of chromic catgut are placed in each fossa, lateral to the rectum. The sutures include the lateral wall of the rectum and the parietal peritoneum of the cul-de-sac. They are tied in pairs in order that the rectum may not be distorted. Two rows of purse string sutures placed about 1 inch (2.5 cm.) apart will obliterate the cul-de-sac. Finally, continuous suture, beginning and ending with a purse string closure, is used to approximate the posterior surface of the broad ligaments to the posterior parietal peritoneum and to close the defect between the anterior surface of the lower portion of the sigmoid flexure and the posterior surface of the uterus.

In the earlier operations a bilateral salpingectomy was done to avoid the possibility of later pregnancy. In recent cases this has been omitted, but care has been taken that the final row of sutures should be placed sufficiently low to avoid impingement on the tubes and ovaries or immobilization of the posterior surface of the uterus. The sutures include the pelvic fascia, but the ureters and the iliac and ovarian ves-

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4. Moschcowitz, A. V.: The Pathogenesis, Anatomy and Cure of Prolapse of the Rectum, Surg., Gynec. & Obst. **15**:7-21 (July) 1912.

Summary of Cases from Feb. 15, 1937 to July 20, 1938

Patient	Sex	Age	Duration of Rectal Symptoms	Degree of Stricture	Pref. Reaction	Formaldehyde Reaction	Wassermann Reaction	Associated Conditions	Date of Operation	Type of Operation	Comment
L. S.	F	20	8-9 yr.	+++++	+++++	—	Negative	Inguinal adenitis (hemoglobin 68%)	2/15/37	Obliteration of cul-de-sac; ligation of tubes; colostomy	7/8/38, stricture practically disappeared; slight hernia about colostomy; hemoglobin 75%
G. M.	F	25	5 yr.	++++	++	—	Negative	Inguinal adenitis (hemoglobin 70%)	7/14/37	Obliteration of cul-de-sac; bilateral salpingectomy; colostomy	
R. S.	F	35	3-4 yr.	+++++	+++++	—	Negative	Rectal fistula, Bartholin's abscess (hemoglobin 80%)	7/27/37	Obliteration of cul-de-sac; appendectomy; colostomy	Stricture relaxing; patient gained 16 pounds (7.3 Kg.); hot enemas and dilations
V. P.	F	60	10 yr. (?)	+++	+++++	—	Negative	Senility; hemorrhoids; rectal abscess; fistula; inguinal adenitis (hemoglobin 60%)	9/25/37	Obliteration of cul-de-sac; oophorectomy, right; colostomy; transfusion	7/8/38, stricture diminishing; hot irrigations and dilations; colostomy closing
E. H.	F	25	5 yr.	++++	*	÷	Negative	Rectal fistula (hemoglobin 47%)	10/1/37	Obliteration of cul-de-sac; appendectomy; colostomy	7/15/38, stricture diminishing; hot irrigations and dilations
G. P.	F	30	2 yr.	+++	++	÷	Negative	Rectal stricture (hemoglobin 65%)	10/27/37	Obliteration of cul-de-sac; colostomy	7/16/38, stricture relaxed; patient gained 11 pounds (5 Kg.); hot irrigations and dilations
M. I.	F	30	8 yr.	++++	++++	÷	++++	Hemorrhoids (hemoglobin 75%)	2/1/38	Obliteration of cul-de-sac; colostomy	5/25/38, plastic operation on colostomy opening; 7/8/38, stricture relaxing; hot irrigations
E. J.	F	25	1 yr.	+++++	*	—	Negative	Rectovaginal fistula (hemoglobin 60%)	2/8/38	Obliteration of cul-de-sac; colostomy	
L. W.	F	27	5 yr.	++	+++	÷	Negative	Proctitis; hemorrhoids (hemoglobin 46%)	5/12/38	Obliteration of cul-de-sac; colostomy; transfusion	7/1/38, proctitis and stricture diminishing
W. M.	M	38	3 yr.	++	+++++	÷	Negative	Proctitis (hemoglobin 62%)	6/22/38	Obliteration of cul-de-sac; colostomy	Patient in hospital at time of this report

* Reaction positive but degree not recorded.

sels must not be injured. Care must be taken to avoid constriction or angulation of the lower portion of the sigmoid flexure, as otherwise a stricture may result at this level.

A "double-barreled" colostomy is then performed through a McBurney incision on the left. The loop of sigmoid flexure is supported by a glass rod passed through the mesentery, and the bowel is opened with the cautery several days later. Ten days after operation the bowel is completely divided, and the glass rod is removed. This separation may be left as a permanent colostomy opening, or the continuity of the bowel may later be restored extraperitoneally at a time depending on the subsequent course of the patient. The infection diminishes after diversion of the fecal current, and the proctitis usually disappears. The stricture softens and responds to dilation. The danger of peritonitis is obviated, and if necessary further local operative procedures, such as the Keller tunnel graft [5] or the Lockhart-Mummery and Lloyd-Davies [6] operation, may be carried out on any part of the rectum with safety.

All of the patients operated on in this series have recovered and have been benefited by the procedure. In 1 of the early cases a small ventral hernia developed at the site of the colostomy. In the later cases greater care has been taken in suturing the aponeurosis of the external oblique muscle through the defect in the mesosigmoid, and no hernia has occurred. In 2 cases the upper segment of the sigmoid flexure retracted beneath the level of the skin, and a plastic procedure was necessary to prevent stenosis of the proximal loop. At present the upper segment is brought out under less tension, and there have been no further strictures.

The statement has been made that the stricture will recur if the continuity of the bowel is restored and the fecal current again passes over the involved segment. I have not closed the colostomy opening in any of my cases and do not know whether the stricture will reform. At the time of this report the stricture in all cases is relaxing, and I feel that the safety afforded by this procedure has already justified its use should no further benefit be derived from obliteration of the cul-de-sac.

The present treatment for strictures due to lymphogranuloma venereum in the Hospital Division of the Medical College of Virginia is as follows:

On admission of the patient a careful rectal examination is made to determine the degree of stenosis, the location of the stricture and the

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5. Keller, W. L.: Annular Stricture of the Rectum and Anus (Treatment by Tunnel Skin Graft), Am. J. Surg. **20**:28-32 (April) 1933.

6. Lockhart-Mummery, J. P., and Lloyd-Davies, O.: Operative Treatment of Fibrous Stricture of the Rectum, with Description of a New Technique, Brit. J. Surg. **23**:19-24 (July) 1935.

extent of fibrosis. If the stricture is within the danger zone and if the index finger cannot be passed without difficulty, further local procedures are deferred until they can be carried out in the operating room under direct vision. The patient is given a diet low in residue but high in vitamin content, and liquid petrolatum is given. A Frei test and a formaldehyde ("formol gel") determination are made. Despite the pathognomonic nature of such a stricture, a small amount of tissue is removed from the posterior wall of the stricture for diagnosis, as cases of carcinoma associated with lymphogranuloma venereum have been reported by Liccione [7] and others. In many cases the patient has been ill for years and is more fragile than she appears. Blood transfusions are given if the value for hemoglobin is less than 60 per cent.

I formerly used antimony and potassium tartrate and (later) fuadin in such cases, without noticeable benefit. Elliott therapy, diathermy and sulfanilamide have been tried, with indifferent success. Hot rectal irrigations and oral administration of potassium iodide appear to allay the discomfort and have given as good results as any other measure.

Several years ago I temporized with this condition and relied on frequent dilations, but the patients did not cooperate well, and the results were unsatisfactory. My tendency now is to obliterate the cul-de-sac and form a colostomy opening as soon as a definite stricture is present. If the proctitis is severe and the Frei test gives a positive result, I feel that a colostomy is frequently indicated before an actual stricture has formed.

The after-care is relatively simple. Rectal irrigations with hot saline solution are given during patient's stay in the hospital, and after his discharge he is instructed to irrigate the diseased segment of bowel by inserting the tip of the syringe into the lower stoma of the colostomy opening. He is directed to return every two weeks to the outpatient department for dilation of the stricture. I have found that the patient returns with greater regularity after the opening has been made than before operation. This is due to the fact that the dilations are less painful after diversion of the fecal current and also to the patient's desire to facilitate recovery in order that the colostomy opening may be closed as soon as possible.

SUMMARY

Ten patients with rectal stricture resulting from lymphogranuloma venereum have been treated by obliteration of the cul-de-sac and colostomy.

7. Liccione, W. T.: Venereal Stricture of the Rectum: Adenocarcinoma as Late Complication, Am. J. Surg. **31**:551-555 (March) 1936.

The closure of the cul-de-sac has permitted dilation of the stricture without danger of peritonitis, and the diversion of the fecal current has resulted in relaxation of the strictures.

If necessary, further operative procedures on the stricture may be carried out through the rectum with relative safety.

This is a preliminary report, for operation in the earliest case was done only eighteen months prior to the time of this report, and none of the colostomy openings has been closed.

Dr. Robert V. Terrell referred most of the patients in this series to the Hospital Division of the Medical College of Virginia and has followed them in the outpatient department since their discharge.

710 Medical Arts Building.

OCCURRENCE, DISTRIBUTION AND PATHOGENESIS OF SO-CALLED LIVER DEATH AND/OR THE HEPATORENAL SYNDROME

ABRAHAM O. WILENSKY, M.D.
NEW YORK

CONTENTS

2. Infections
   A. Bacteremia
   B. Special forms of bacteremia (tularemia)
   C. Local bacterial infections
   D. Spirochetal infections
   E. Undifferentiated infections
3. Various forms of poisoning or intoxication
   A. Conditions due to pregnancy
   B. Thyrotoxicosis
   C. Poisoning by drugs and chemicals
4. Conditions accompanying massive destruction of cellular tissue
5. Hemolytic jaundice
6. Undifferentiated jaundice; icterus gravis
7. Acute yellow atrophy of the liver

III. Incidence of lesions in the liver and kidneys and/or of symptoms of the hepatorenal syndrome as related to associated and/or accompanying factors common to many of the hereinbefore mentioned conditions
   1. Effect of high temperature per se
      A. Pathologic effects of fever therapy
      B. Pathologic effects of heatstroke
   2. Effect of the various forms of anesthesia
   3. Effect of anoxemia; anoxia
   4. Effect of shock and shocklike states
      A. Neurogenic shock
      B. Traumatic shock
      C. Shock following hemorrhage
      D. Hemolytic shock
      E. Peritonitic shock
      F. Shock associated with acute intestinal obstruction
      G. Anaphylactic shock
      H. Shock produced by action of toxin
      I. Shock produced by chemicals
   5. Effect of dehydration and anhydremia
      A. In pediatric practice
      B. In surgical practice
      C. Accompanying autolysis of tissue
      D. Accompanying peritonitis and intestinal obstruction
      E. Accompanying water starvation on the desert
   6. Effect of autolysis of tissue
      A. In strangulation ileus
      B. In traumatic destruction of tissues
      C. In necrosis of tissue following operation (unexpected)
      D. In burns
      E. In gangrenous inflammations
      F. In radium necrosis
      G. In necrosis in tumors
      H. In experimental work
   7. Effect of acute peritonitis

IV. Experimental production of lesions in the liver and kidneys

    1. Traumatic destruction of parts of the liver

    2. Interference with hepatic and portal circulation

    3. Obstruction of the biliary tree

    4. Injection of extracts of damaged liver

        A. By biliary obstruction with and without sudden release

        B. By injection of various chemicals

        C. By disease or operation ("liver death")

    5. Implantation or injection of normal liver and/or an extract of normal liver

Comment

    Physiologic, complementary and clinical associations of liver and kidney

    Phylogenetic relations of liver and kidney

    Distribution of similar degenerative lesions in other parenchymatous organs

    General similarity of lesions

    Occurrence of hepatic and/or renal lesions clinically

    Nonspecificity of hepatorenal lesions and/or symptoms

    Similarity of effect produced by a variety of causes

    Associated general constitutional or other factors complicating hepatorenal lesions

    Hyperacute, hyperpyrexic form—so-called liver death

    Relation of the hyperacute hyperpyrexic form (so-called liver death) to the delayed clinical and pathologic manifestations in the so-called hepatorenal syndrome

    Hepatic lesions

    Relation of the hepatorenal syndrome to disease of the liver and the biliary tract and the cause of its inception

    Value of tests of hepatic function and/or damage

    Renal element and the value of functional tests

    Effect of the excretion of bile through the kidneys

    Relation of the renal to the hepatic lesion

    Disturbance of renal function

    Renal lesions in the presence of demonstrable azotemia

    Clinical value of tests of renal function and of estimations of the extent of azotemia

Summary

INTRODUCTION

Coincident with the repeated calling of attention to the interrelation of the liver and the kidneys in the determination of fatal outcome of operations on the gallbladder and biliary tract, a diversity of opinion has developed regarding the so-called hyperpyrexia liver death and the hepatorenal syndrome. Indeed, by certain authors (Heuer and others) the statement has been made that in all the cases observed by them at autopsy other causes which could adequately account for the clinical phenomena and the fatal outcome were demonstrable. Other observers (Boyce, Boyce and McFetridge, Stanton, Connell and others) have stated the opinion that the condition is more common than the references in the literature seem to indicate.

In this communication I shall attempt to assemble all available experience, shall examine, correlate and evaluate all the available apparent and discoverable factors, shall attempt to establish the accuracy of the prevailing assumptions in regard to this syndrome and shall, finally, attempt to find the cause and mechanism of this biologic progression.

CLINICAL TYPES

Two distinctive clinical pictures have been described: (1) that in which the outstanding symptom is hyperpyrexia occurring immediately after operation and leading quickly to death and (2) that of delayed death, associated with the hepatorenal syndrome.

HYPERPYREXIA DEATH

Hyperpyrexia has in certain quarters been correlated with the concept of so-called liver death.

There is a wide disparity of opinion concerning the incidence and nature of postoperative high temperature death. The phenomenon is not confined entirely to operative cases of disease of the liver and the biliary tract. For instance:

Crisp reported a case observed at the Mayo Clinic, in which "high temperature death" followed resection of the rectum for malignant tumor. There was no demonstrable evidence of peritonitis at this early stage, and the observers eliminated the possibility of surgical shock; there was marked evidence of extreme toxicity.

Since 1931 Connell has changed his opinion and in 1934 he reported 3 interval appendectomies, 1 laparotomy for ovarian cyst and 1 hysterectomy, after all of which high temperature death occurred. DeCourcy in 1937 reported 2 operations which were followed by high temperature death; 1 was a colostomy and the other a hysterectomy.

Boyce and McFetridge reported the case of a Negress on whom a resection of the cecum was done for acute typhlitis. The patient died within seventy-two hours, in hyperpyrexia. The nonprotein nitrogen content of the blood was 72 mg. per hundred cubic centimeters, in contrast to a preoperative level of 29 mg. Postmortem examination eliminated the presence of peritonitis or other surgical complication and showed hepatorenal changes typical of the hepatorenal syndrome. The same authors reported a second case, in which these clinical and anatomic changes were observed in association with carcinoma of the pancreas with metastases in the liver.

In my own experience with intestinal obstruction and especially with the operative release of a comparatively old intestinal obstruction (obstruction of forty-eight to seventy-two hours' duration) I have seen quick death associated with immediate postoperative hyperpyrexia on a number of occasions. For instance:

A child aged 9 months was admitted to the hospital with a typical picture of acute intestinal obstruction of approximately twenty-four hours' duration, due

an acute intussusception. The child was immediately operated on, and during the operation the intussusception was easily reduced. The entire operation took about ten minutes. During the next eighteen hours the temperature rose to above 106 F.; tremendously toxic symptoms developed, and the child died. Postmortem examination showed negligible changes in the liver and some slight degenerative changes in the kidney. There was no time for chemical, bacteriologic or other laboratory studies before death occurred.

Cases of liver death are especially disconcerting, as with other types of disease one usually deals with very sick persons or with those requiring the severer types of operation, in which, so to speak, almost anything can happen. In these cases one begins usually with a patient who shows no signs of jaundice and is in good condition. The problem is relatively simple, and operation usually proceeds without any alarming occurrence. Then comes an immediate and progressive rise of temperature; disturbances of the sensorium quickly pass on to lethargy and coma; signs of excessive nervous irritability (carphologia and subsultus tendinum) appear; the patient is obviously very sick and then moribund, and death occurs within from twenty-four to forty-eight hours.

At postmortem examination one is disappointed at the anatomic observations. The hepatic cells show signs of disorganization or beginning destruction; occasionally the kidney shows some congestion, and rarely similar degenerative changes are seen in the renal cells. As far as I know, no bacteriologic studies have been reported; but in my own experience blood culture in such cases has frequently been negative. Nevertheless, it is not possible to brush aside the question of infection as the true cause of death.

The explanation of the clinical phenomena is especially difficult when one compares such a case with a case of postoperative acute cholangitis. Many patients for whom acute cholangitis is a new postoperative condition or an extension and exaggeration of a preceding lesion show high fever and marked toxicity immediately after operation. Death within twenty-four to thirty-six hours after operation is common. So far the resemblance of the clinical manifestations is exact; and if one were limited to this information, it would be hard to classify postoperative cholangitis anywhere but with hepatorenal disease. In the presence of acute cholangitis, however, blood culture is frequently positive, the pathologic picture in the liver differs in that acute inflammatory foci are present around the ducts. as opposed to degeneration of the central hepatic cells. and abscesses are common. It becomes apparent, then, that no matter what the clinical manifestations may be, the lesions are sharply divorced even though both are necessarily within the liver.

Another disturbing element in the concept of liver death is the fact that in many cases in which symptoms suggestive of liver death were present before death. postmortem examination revealed exclusive or

additional causes entirely competent to produce death with high tempera-
ture; commonly the cause was found to be a subphrenic peritonitis or
abscess which had escaped diagnosis. Touroff has reported a series
of such cases.

It is instructive to compare the phenomena in cases of liver death
with similar phenomena in those of outstanding infection:

A young man was admitted to the hospital with the diagnosis of "chronic appen-
dicitis," and appendectomy was done. During the next thirty-six hours the
temperature rose to well over 106 F.; the patient showed marked signs of toxicity,
and death occurred. Postmortem examination showed peritonitis, distinctive but
yet in an early stage of development, and there were inconspicuous changes in
the hepatic and renal cells.

Another young man was admitted with chronic osteomyelitis of the femur,
and osteotomy was done. Prior to operation there was no fever, and there was
no reason to think that bacteremia was present. Nevertheless, operation was fol-
lowed immediately by a progressive rise in temperature, by increasing signs of
general infection, by a growth of bacteria in the blood culture and by death within
seventy-two hours. Postmortem examination showed the usual changes incident
to a general infection but no special morphologic changes in the liver or the kidney.

Almost any surgeon of experience can duplicate experiences of this
kind. Many experiences have shown that infection can reproduce
clinical pictures almost exactly similar to those associated with liver death.
I do not believe, however, that any physician of experience would say that
in the cases just described or in any case of similar involvement the
outcome was liver death.

HEPATORENAL SYNDROME

Patients with the delayed hepatorenal syndrome show a clinical picture
which is fairly characteristic. The manifestations develop slowly. In
a few cases the symptoms are mild and consist in increasing mental
lethargy, gastrointestinal symptoms and diminished output of urine.
There may be a variable degree of retention of nitrogenous bodies in
the blood stream. Under the influence of the introduction of large
amounts of fluids containing sugar and salt and occasionally of whole
blood, the picture quickly rights itself, the laboratory findings return
to normal and the patient recovers. It is difficult to determine how often
this clinical picture develops, as unless one is on the watch for it the
symptoms are likely to escape notice among the clinical phenomena
which commonly follow serious abdominal operations.

In the most severe grade of disturbance there is no regression. The
clinical subjective and objective symptoms increase in severity; the
lethargy passes into coma; the gastrointestinal symptoms become more
marked; the output of fluid from the kidneys steadily diminishes until
in some cases there is virtual suppression of urine; carphologia, sub-
sultus tendinum and occasionally convulsions appear, and death follows

shortly. In such cases jaundice is a common objective symptom. It is likely to appear in cases in which the phenomenon has not previously been present. In many cases, especially if the condition is severe, intestinal or other hemorrhage is described as an important symptom.

Between these extremes all grades of disturbance occur. In most cases the condition progresses quickly to a fatal termination; a few patients recover. The essential discoverable factors which appear to enter into the formation of the hepatorenal syndrome are degeneration of the hepatic cells and similar degeneration of the renal tubular epithelium. In no case is there any other satisfactory explanation for the hepatorenal syndrome and/or symptoms or for the fatal issue.

The hepatic parenchyma shows the following changes: About the central veins the hepatic cells show some shrinkage and cytoplasmic granulation. Between many of the cells of the lobule the biliary canaliculi and capillaries are plugged with pigmented material. Various degrees of necrotic change are observed in the hepatic cells, especially in those of the inner central portion of the lobule of the liver and about the larger bile ducts. The stellate cells of Kupffer are swollen and seem to show increased activity.

Helwig and Orr described accurately the anatomic changes in cases of trauma. There are large areas of hemorrhage in which no viable hepatic cells are present. Amorphous shadows, staining with the typical outline of hepatic cells, are found in masses in the hemorrhagic areas. The destroyed areas in the livers of patients who live long enough show evidences of attempted healing by scar tissue and of reformation of biliary canaliculi. Peripheral to the destroyed areas and surrounding the reparative areas the liver resembles that seen in cases in which no trauma has occurred.

Helwig and Orr emphasized resemblances seen in this anatomic picture to that observed in the presence of eclampsia.

The following changes are found in the kidneys: In the cortex, the convoluted tubules and the loops of Henle show extensive parenchymatous degeneration. Many tubules contain only two or three recognizable nuclei which are pale and hazy and are apparently undergoing lysis. Some tubules seem to have undergone complete necrosis. The epithelial cells of the differentiated tubules are frequently pigmented with fine greenish granules. The epithelium lining Bowman's capsule is swollen, and red cells are scattered about, surrounding the capillary tufts. In the capillary loops the endothelium is swollen, and a few polymorphonuclear leukocytes are scattered in the capillary channels. Cloudy swelling, granular, albuminous precipitate and pale casts are seen in the collecting tubules. Some attempts at regeneration of the renal epithelium are observed. In cases of trauma evidences of hemorrhage

and of the results of hemorrhage abound. These changes are surely related to the original trauma and not to the regenerative changes.

Hepatorenal lesions and/or symptoms are found under many diverse conditions in clinical medicine, and a careful factual examination of all of them is the physician's first problem. A summary of all the conditions in which hepatorenal lesions and/or symptoms have been found and described follows.

I. CLINICAL INCIDENCE OF HEPATORENAL SYNDROME AND/OR LESIONS AS RELATED TO SPECIFIC ILLNESSES OR GROUPS OF ILLNESSES AND TO ABNORMAL PHYSIOLOGIC STATES, CONDITIONS, ETC.

INCIDENCE IN RELATION TO DISEASE OR INJURY OF THE LIVER AND THE BILIARY TRACT

1. Disease of the biliary tract without jaundice, is almost always associated with cholelithiasis and occurs usually in patients over 40 years of age and more or less obese. Most of the patients, in spite of any coincident and/or associated cardiac and/or metabolic disturbances (hypertension, myocarditis, disease of the coronary artery or diabetes) are satisfactory operative risks, and operation is undertaken with no trepidation. The following three factors are elicitable in such cases: a lesion of the biliary tract (calculus and/or infective cholecystitis), postmortem evidence of degeneration of hepatic cells and postmortem signs of renal tubular degeneration.

2. With some patients the disease described in the foregoing paragraph is associated with a pancreatic factor, evidenced by a thickening of the head of the pancreas and sometimes by enlargement of the lymph glands which normally drain the pancreas. Heyd and also Boyce and McFetridge have called attention to this condition.

3. Obstructive jaundice of nontraumatic origin is commonly associated with disease in the biliary tract, most frequently brought about by cholelithiasis and profoundly aided by infection extending upward in the biliary tree. The one additional factor appearing in this disease, which precedes the development of the hepatorenal syndrome, is jaundice.

4. Similar conditions prevail when the obstruction is due to malignant growths, which occur most frequently at the papilla of Vater and the head of the pancreas and less frequently at various sites of the larger biliary ducts proximal to the papilla of Vater. Here, however, a new factor is introduced, namely the malignant growth; and in the light of present knowledge, it must be assumed that the cause of death can be one of two. In some cases death seems to be due to the same facts and events as in cases of obstructive jaundice; in the larger proportion

however, the mechanism of death seems to be no different from that of death caused by malignant tumor in other parts of the body in which the hepatorenal factor is not present.

Conditions similar to those described in the foregoing sections have occurred after various operations on the biliary apparatus as well as when no operation has been performed.

5. In 1927 Furtwaengler reported a case from Clairmont's clinic in Zurich, Switzerland. The patient was a 22 year old woman who had been hurt in an automobile accident. A crushing injury of the liver was present. Jaundice did not develop. A clinical picture exactly similar to that usually seen when the hepatorenal syndrome is present followed, and death occurred three days later. Postmortem examination showed bilateral necrosis of the renal cortex in addition to the hepatic destruction. The series of cases of fatal disease of the biliary tract following operation collected by Stanton in 1930 included 1 in which the involvement was similar in all respects to that described by Furtwaengler.

6. In 1932 Helwig and Orr reported the case of a 15 year old boy who after traumatic pulpification of the liver showed extreme jaundice, diffuse hemorrhages in the serous cavities, scantiness of the urine and an increase in the nitrogenous elements of the blood, especially in creatinine. The typical hepatorenal syndrome developed. The patient lived eleven days. Postmortem examination showed, in addition to the destruction of hepatic cells, extreme degeneration and destruction of the renal tubular epithelium.

A picture similar in all respects to that in the cases of Helwig and Orr and of Furtwaengler was also described in 1935 by Boyce and McFetridge, from the Charity Hospital in New Orleans. Their experience included 6 cases, in some of which operation was performed.

The conditions described in the two sections immediately foregoing present the additional factors of a crushing injury of the liver and of pulpification of hepatic cells and tissue. Compare these data with those presented in the section on the effects of autolysis of tissue, which follows.

INCIDENCE IN RELATION TO OPERATIONS FOR OTHER CONDITIONS

In addition to such cases as those previously described, the literature contains a number of reports of cases in which the hepatorenal syndrome followed abdominal and other operations in which the liver and biliary tract were not primarily involved. For instance, Schutz, Helwig and Kuhn reported a group of 6 cases, in 1 of which the syndrome developed eleven weeks after an operation for carcinoma of the breast: they mentioned also a case reported by LeNoir and his associates, in which, after an operation for gastric ulcer, similar symptoms developed and the patient died. Other cases were referred to elsewhere in their communication.

INCIDENCE IN RELATION TO CONDITIONS ORIGINATING
OUTSIDE THE LIVER OR BILIARY TRACT

Symptoms similar in all respects to those composing the hepatorenal syndrome are known to develop as a result of other conditions which have nothing in common with hepatic disease primarily and in the absence of any such conditions of the liver and biliary tract as have been described. The clinical, pathologic and anatomic study made by Rindone of 60 patients with complaints referable to the right side of the abdomen showed that the liver is always involved in the "right abdominal syndrome," whether simple or complicated. The involvement is inflammatory and degenerative, and the amount of damage is proportional to the severity of the symptoms. Rindone expressed the opinion that the anatomic changes result from toxic or bacterial products absorbed through the portal vein. These findings and Rindone's opinion were confirmed by Bombi, who studied this relation with special reference to the chronic forms of appendicitis. The syndrome may be associated with such widely diversified conditions as drug and chemical poisoning, thyrotoxicosis, pregnancy and intestinal obstruction. Indeed, Rowe, studying nearly 4,000 cases of various diseases, found the incidence of hepatic involvement, even including figures which he considered to be "heavily overweighted," to be approximately 10.91 per cent.

The following is a summary and description of these conditions:

1. *Toxic Effects of Drugs and Chemicals.*—A. A large·number of drugs and chemicals are known to produce characteristic changes in the hepatic cell, leading to degeneration and necrosis. The list of these has been materially increased by addition of many newly synthesized drugs. The effect of anesthetic drugs (see section on anesthesia) is related to this syndrome in the effects on the hepatic cell. The most important of these drugs is chloroform. Hanner and Whipple showed experimentally that chloroform and phosphorus produce identical characteristic lesions in the liver. The case of apiol (parsley camphor) poisoning reported by Thiers, which terminated in death with the hepatorenal syndrome. seemed to be an instance of this sort. During the war anatomic pictures of necrosis of hepatic cells approaching the appearance of "acute yellow atrophy" of the liver were frequently observed as a result of the absorption of chemicals employed in the manufacture of explosives and other military supplies, especially trichlorethane and trinitrotoluene. Similar toxic effects were seen during prohibition. following the consumption of varnish removers, hair tonics, cleaning fluids and similar chemicals. which were taken for their intoxicating effects as follows:

B. Similar effects on the hepatic cell have been reported as follows the use of preparations containing cinchophen and some of its derivatives.

Among these Rabinowitz listed the following:

Agotan ⎫
Atophan ⎪
Quinophan ⎬ (cinchophen)
Phenylcinchoninic acid ⎪
Neocinchophen ⎭

Novatophan ⎫
Tolysin ⎬ (neocinchophen)

Atophanyl (sodium cinchophen combined with sodium salicylate and pro-
caine hydrochloride)

Diiodoatophan ⎫
Biloptin ⎬ (a combination of iodine and cinchophen)

Oxyliodide (a preparation of cinchophen hydroiodide)
Phenoquam (a cinchophen preparation)
Leucotropin (a compound of methenamine and cinchophen)
Atrophan-urotropin (a combination of cinchophen and methenamine)
Fantan (a urethrane-cinchophen compound)
Iriphan (a strontium salt of cinchophen)
Weldona (a compound which contains, or has contained, cinchophen)
Farastan (monoiodocinchophen)
Atoquinol (allylphenylcinchonic ester)

Rabinowitz reported from Kessel's service at the Mount Sinai Hospital the case of a woman aged 51, who for arthritis, nasopharyngitis, infected tonsils and obesity had undergone a tonsillectomy in March 1929. The operation was followed by prolonged administration of sodium salicylate, iodides and cinchophen. After four weeks the patient was bedridden and jaundiced. She became comatose and more deeply jaundiced; pitting edema of the ankles was observed, and the liver felt small to percussion. A provisional diagnosis of acute yellow atrophy of the liver was made. The patient died. Diagnosis at autopsy was subacute yellow atrophy of the liver; jaundice; edema of the ankles; parenchymatous degeneration of the heart and kidneys; tracheitis and bronchitis; obesity, and hemorrhages in the skin and mucous membranes of the intestine, the trachea and the bronchi.

Cabot stated that in cases of cinchophen poisoning observed at the Massachusetts General Hospital "there were distinct degenerative changes in the tubular epithelium of the kidneys, though similar changes were more marked in the liver."

In the cases reported by Palmer and associates there were outstanding pictures of acute yellow atrophy (toxic necrosis) of the liver. Palmer has given me the incidence and character of the accompanying renal lesions, as classified by his house officer, Lyman:

	Cases
Acute parenchymatous degeneration	9
Chronic nephritis with acute degeneration	1
Acute toxic tubular nephritis	1
Parenchymatous degeneration with biliary pigmentation	2
Bile staining	3
Chronic passive congestion	2
Glomerulonephritis	1
Fatty degeneration	2
Arteriosclerotic scarring	2
No change noted	1
Total	21

This summary gives a good view of the extent of the tubular and parenchymatous renal degeneration which accompany the hepatic lesions in cases of cinchophen poisoning.

C. Another of the newer drugs is germanin. Veiel introduced it in 1931, in the treatment of pemphigus vulgaris. Autopsy reports either on human beings or on experimental animals treated with germanin are few and incomplete. Nevertheless, there is evidence of a tendency to hemorrhage, to the formation of areas of focal necrosis with fatty changes in the liver and to constant and striking epithelial degeneration with necrosis in the renal tubules.

D. Identical pathologic changes in the liver and kidneys follow the use of peptone, histamine and albumose. The work of Hofbauer suggested that these substances might have some relation to the "eclamptic" conditions of pregnancy; the existence of any such association was disproved, however, by Stander. According to the latter author, these substances produce degenerative changes in the liver, involving the greater part of the lobule and leaving free only a rim of normal cells about the periphery. The condition is, therefore, strictly speaking, central necrosis, whereas in the presence of eclampsia there is typical peripheral necrosis.

E. A large group of compounds has developed since the introduction of arsphenamine for the treatment of syphilitic conditions. Extensive lesions occur, approaching those of acute yellow atrophy of the liver. Best has collected over 400 cases.

Heyd has reported 1 case in which death occurred during coma from hepatic degeneration, with "intense nonobstructive" jaundice which he attributed to arsenical poisoning.

F. The newest drugs to produce this syndrome are sulfanilamide and an elixir of it made with diethylene glycol. Studies were made under the auspices of the American Medical Association as a consequence of reports of a number of fatalities following the use of this drug. Microscopically the most marked changes have been observed by Cannon in the kidneys and liver. The epithelium of the convoluted tubules shows intense hydropic degeneration, sufficient to block the lumen and to alter the normal structure. In some animals necrosis caused disappearance of the cells. The collecting tubules are relatively unchanged. In addition, the glomerular tufts show shrinkage, although the blood channels are still patent and full of blood. The general picture is that of severe chemical nephrosis. The hepatic cells show similar changes, with the bulk of the lesion around the central veins; the necrosis is not severe, and leukocytic infiltration is minimal. The changes are not caused by sulfanilamide alone. Kesten, Mulinos and Pomerantz showed that the lesions may be produced by diethylene glycol alone.

2. Toxemia of Pregnancy.—The normal anatomic changes in the liver produced by pregnancy are: (1) increase in the weight of the organ (only in animals) and functional hypertrophy, which does not occur in the kidneys; (2) decrease in glycogen, which is not constant, and (3) fatty infiltration of the central lobes of the liver (venous and biliary stasis). Formerly the latter two changes were thought to indicate insufficiency, but today this theory is difficult to reconcile with the view that they are physiologic processes.

In pathologic states complicating pregnancy a number of clinical entities have been gathered under the generic term of "eclamptic states," "preeclamptic states" or "toxemia of pregnancy." They occur either early or late in pregnancy; clinically they are characterized by pernicious vomiting, nervous and mental changes, anemia, epigastric pain and tenderness, hypertension, albuminuria, eylindruria, bilirubinemia, azotemia and convulsions.

Typical toxemic states ("eclamptic" or "preeclamptic" states) may follow glomerulonephritis, pyelitis, pyelonephritis or vascular hypertension, which in turn may be complicated by secondary nephritis. Practically speaking, these are examples of "nephritis" complicating , pregnancy or of a primary cardiovascular lesion in which "nephritis" supervenes and complicates the pregnancy. This aspect of the problem is of no present concern except in the similarities of the conditions to the hepatorenal syndrome.

Pathologic lesions in the liver, as well as functional impairments, are found only irregularly during pregnancy and seem unrelated to the previously described renal and cardiovascular conditions. According to Heynemann, mild pathologic conditions of the liver occurring during pregnancy are usually of an easily reversible nature, and possibly their incidence exceeds that of renal and cardiovascular lesions. Clinically they are apt to appear as cases of hyperemesis, infection, catarrhal jaundice (various forms of cholangitis) and intestinal intoxication. The transition of any mild condition into a severe one is relatively and actually rare, according to Heynemann. Severe disease of the liver approaches more and more, in accordance with its severity, "the picture of acute yellow atrophy of the liver."

Pathologically, scattered areas of hepatic lobular necrosis appear with some frequency in a certain proportion of cases of pregnancy complicated by "toxemia." It is to be noted that in pregnant patients necrosis of the hepatic cells begins in the periphery of the lobule and increases progressively toward the center, whereas in nonpregnant patients presenting the hepatorenal syndrome the cellular necrosis begins in the center of the lobule and spreads toward its periphery. According to Peters: "The histological changes found in the tubules and glomeruli

of a large proportion of patients who die in the acute stages of toxemia, whether they had eclamptic seizures or not, have certain features which distinguish them from the lesions commonly found in acute nephritis." Bell and others expressed the belief that these differences are distinctive.

Metabolic changes during pregnancy, as evidenced by the study of the body fluids, are only suggestive. Although the sugar content of the blood during toxemia seldom falls to extremely low levels, some of the neurogenic symptoms have been ascribed to hypoglycemia. The non-protein nitrogen content of the blood during the later months of pregnancy tends toward a low level; according to Peters, figures of 40 mg. per hundred cubic centimeters are commonly obtained at such a time. The urea nitrogen fraction should therefore not be interpreted as being only at the upper limits of normal but should be considered to indicate a considerable increase over normal for the pregnant woman.

There are enough clinical and anatomicopathologic manifestations in such conditions to make out an entity in which the liver and the kidneys play important parts. The resemblances are marked enough to make one take some of these toxemic states seriously into account in considering the hepatorenal syndrome.

The resemblance is accentuated by the following remarkable fact: In a certain proportion of cases eclamptic manifestations seem to be precipitated by labor and/or to follow immediately after delivery. This fact calls forcibly to mind the similar precipitation of manifestations which follows the release of obstruction in the biliary ducts or in the intestinal canal. It seems that a similar mechanism must function in each of these states (vide infra).

3. *Thyrotoxicosis.*—Hepatic lesions develop in a fair percentage of cases of hyperthyroidism and are followed by terminal renal changes which closely approximate the changes seen in the presence of the hepatorenal syndrome. As opposed to the finding that 10.91 per cent of 4,000 patients with various diseases showed hepatic lesions, Rowe found that hepatic disease follows hyperthyroidism in 22.44 per cent of cases. Lahey has commented on the close similarities between the hepatorenal syndrome observed in the presence of hyperthyroidism and that observed in the presence of primary pathologic conditions of the liver.

Numerous references to the association of icterus with thyrotoxicosis are found in the literature, beginning with that of Habershon in 1874 and continuing with those of Eger, Sutcliff, Eder, Sattler and others. Assmann distinguished one group of cases in which icterus resulted from cardiac insufficiency. In another group Assmann placed those cases, chiefly instances of severe general toxicosis and rapidly lethal outcome, in which the more severe conditions passed into acute yellow atrophy of the liver. Such conditions, he stated, were probably related etio-

logically to the preceding hyperthyroidism. Kerr and Rusk in 1922 reported a case of hyperthyroidism in which autopsy revealed what amounted to acute yellow atrophy of the liver, with marked parenchymatous changes in both the liver and the kidneys, and in a paper written in 1930 Kerr mentioned several cases of somewhat similar disease observed since then.

Boyce and McFetridge were impressed with the occurrence of the hepatorenal syndrome in association with disease of the thyroid gland. They emphasized the fact that the renal aspect had not been particularly stressed before their report. Weller also investigated this aspect of the problem extensively. At autopsy in 44 cases of hyperthyroidism he found evidence of marked hepatitis in 22 and of moderate hepatitis in 16, while in only 6 cases in the series was the liver normal. In a control series of cases of other conditions he noted precisely reverse conditions, that is, 30 cases in which there was no evidence of hepatic involvement, 13 of slight involvement and only 1 of marked involvement.

Lahey emphasized the fact that deaths associated with hyperthyroidism are chiefly liver deaths, as is proved by the terminal jaundice sometimes present, by the development of hyperpyrexia without infection and even before operation, and by the benefit, achieved with measures commonly used to combat hepatic damage, chiefly infusions of dextrose, forcing of fluids and transfusion.

Definite autopsic evidence of hepatic damage in thyroid disease has been furnished by a long list of observers and experimenters, including Weller, Kerr and Rusk, Hashimoto, Goodpasture, Beaver and Pemberton and Cameron and Karunaratne.

Experimental work along this line has been reported by Schryver (1905), Cramer and Krause, Parhon, Kuriyama, Fukui, Reinwein and Singer, Dresel, Goldner and Himmelweit, Simonds and Brandes, Hewitt, Hoskins, Farrant, Eger, Marine and Lenhart, Landau and Hashimoto. Numerous pathologic anatomic pictures have been described, showing the characteristic changes in the hepatic parenchyma. Bartels and Perkins' work on the hippuric acid test for hepatic function indicated that in many cases mild hepatic dysfunction or disturbance occurs, which without the use of this test might escape notice.

Indubitable proof was advanced experimentally by Hashimoto in 1921, his experiments being confirmed by Goodpasture in the following year. These workers fed albino rats with thyroid substance in an endeavor to reproduce the myocardial changes observed in human patients with disease of the thyroid, and they reproduced not only those changes but parenchymatous changes in the liver and in the convoluted tubules of the kidneys.

Maes, Boyce and McFetridge have called attention to the fact that a practical application of this knowledge has been emphasized by C. H. Frazier and his associates Brown and North, and by W. D. Frazier and Frieman, who have repeatedly pointed out the importance of intravenous administration of dextrose as a prophylactic measure against postoperative thyroid crisis and have furnished convincing statistical proof of their claims.

The first clinical observation of a condition which might properly be considered acute yellow atrophy in association with exophthalmic goiter was that of Kerr:

The patient was a man aged 39, who first showed icterus on the fourteenth day after bilateral partial thyroid lobectomy for hyperthyroidism. Hepatic dulness was diminished, and bile was present in the urine. Death occurred two days later. At autopsy a diagnosis of "hyperplastic goiter with chronic interstitial strumitis" was established. The liver weighed 1,290 Gm. Its surface was coarsely granular and light brownish red. On section the normal structure was obscured, and the color was opaque reddish brown, with numerous scattered hemorrhagic blotches. On microscopic examination almost complete loss of the normal architecture was observed. In the periportal regions there was diffuse infiltration with lymphocytes and some plasma cells. Beyond (central to) these lymphocytic masses were areas showing the remains of necrotic hepatic cells, infiltrating lymphocytes and leukocytes and hemorrhage. The illustrations accompanying the description showed extensive necrosis of the parenchyma and fully justified the clinical diagnosis.

In the year after publication of the first report by Kerr, Raab and Terplan described a case of similar disease under the title "Basedow's Disease with Subacute Yellow Atrophy."

Loss of weight, weakness, vomiting, rapid and sometimes irregular pulse and icterus had marked the clinical course. After death the liver weighed 1,160 Gm.; its consistency was reduced; the cut surface was diffusely yellow, with dark red areas, and the periportal and interacinar connective tissue stood out in relief. Microscopic examination showed extensive necrosis, lipoidosis, deposits of bile pigment and new-formed bile ducts gave evidence of round cells and leukocytes in the necrotic areas. Fibroblastic proliferation and new-formed bile ducts gave evidence of attempted repair. The entire picture was that "which may properly be called subacute acute yellow atrophy of the liver."

Barker also has described atrophy and necrosis of the liver in connection with severe thyroid intoxication.

Mora has recently summed up the relation of thyrotoxicosis to pathologic conditions of the liver.

Hepatic changes appear to be an integral part of the syndrome of thyrotoxicosis. This can be demonstrated clinically by the occurrence of icterus; physiologically, by the increasing evidence of altered hepatic dysfunction; experimentally, by the evidence of hepatic dysfunction following administration of thyroid substance and thyroxin; and morphologically by structural changes in the liver, varying in the acute stages from widespread degenerative, fatty and necrotizing processes to

the chronic lesion in which the changes are interlobular, irregularly distributed, involving the peripheral portions of the lobule and showing relatively more fibrosis and lymphatic infiltration than bile duct proliferation.

Weller informed me that there are no constant renal lesions in cases of thyrotoxicosis. "Many of the patients showed varying degrees of cloudy swelling and a few fatty changes, but these degenerative changes were no different in kind or degree from those seen in many other conditions." I do not agree with his assumption, in view of the facts which are gradually coming to light, that "no significance should be attached to them"; I am, rather, of the opinion that such changes indicate the general trend of renal lesions to accompany and/or follow degeneration of hepatic cells.

4. *Burns.*—The facts and phenomena and the pathologic anatomic changes following or accompanying death caused by the physical agency of heat (fire or boiling fluids) are as follows:

There is an immediate intense systemic disturbance, customarily termed "shock," the evidences of which (depression of all vital processes and low blood pressure) are too well known to warrant repetition. In some cases death results either immediately or within the first twelve hours; it may occur from small or mild burns as well as from those of larger extent. Hyperpyrexia is frequently present. In such cases Wilson and his co-workers were able to demonstrate infiltration of the liver and sometimes of the other organs with eosinophils. The clinical progression includes (*a*) vomiting, frequently of bloody material from erosions in the upper reaches of the alimentary tract, (*b*) drowsiness, passing into coma, (*c*) convulsions (in children) and (*d*) death.

This initial period is followed by a second period, lasting approximately five days, in which the clinical phenomena are those of some form of toxemia. Death also occurs frequently during this period. There have been a number of explanations for this toxemia:

a. Underhill and his associates have attributed it to an increased concentration of the blood, producing circulatory embarrassment.

b. Aldrich concluded that it is caused by bacterial infection in the burned area.

c. Clark and Cruickshank, in the report of the Mines Department in England, tended to show that both loss of fluid and infection operated in producing the toxemia.

d. The report of Wilson and his group denied the accuracy of these observations. These investigators showed that the concentration of fluid played no role, because the clinical signs were aggravated by the intravenous administration of fluids. They disproved the infectious theory by showing that cultures of the fluid which accumulates in the tissue below the burned area are commonly sterile: and in the few cases in

which it was possible to cultivate hemolytic streptococci from this fluid there were no signs of intoxication.

According to Keschner and Klemperer, there is a relatively high incidence of hepatic edema [1] in cases of death following burns; the experience of these two observers confirmed that of Eppinger.

The postmortem studies made by Agnes MacGregor (one of Wilson's group) showed characteristic changes in the liver in cases of death after burns. Areas of necrosis occurred in the centers of the lobules of the liver, with fatty degenerative changes. The tubules of the kidneys also showed degeneration, but the changes were less severe and less constant than were those in the liver. In some instances there were similar changes in the brain cells. In Weiskotten's cases hemorrhages occurred in the adrenal glands, and in Bardeen's cases there was so-called focal necrosis in the lymphatic tissue.

Wilson's group of investigators also observed 5 cases in which a form of "toxic" jaundice appeared, beginning about the fifth day after the burn occurred. The van den Bergh reaction was biphasic. There were no signs of bacterial infection in 2 of the cases.

In their studies Wilson and his group came to the conclusion that the hepatic changes associated with toxemia caused by burns are due to some toxin circulating in the blood and becoming concentrated in the liver. Experimentally, fluid from the burned area exhibited the same toxicity, and the animals died within twenty-four hours. Wilson expressed the belief that the toxins result from a slow autolytic change in the burned area and that possibly the action of the toxin is augmented by the products of bacterial infection. Curiously enough, the toxemia following burning of tissues is similar to the toxicity which has been observed to result from traumatization of tissues; and the augmentation by bacterial growth recalls the effect of symbiotic growth of bacteria in the presence of gas gangrene and in non-gas-producing forms of gangrene of the abdominal wall.

According to Duval, the clinical picture, the humoral changes and the local (cutaneous) and visceral lesions observed in the human being, when considered in the light of the results of animal experiments, lead to the conclusion that this phase of intoxication or toxemia is general and is due to the absorption of toxic products formed in the burned area. It is similar up to a certain point to the symptoms and lesions of toxemia produced by organic (diphtheria, typhoid) or chemical (pyridic bases)

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1. Rössle maintained that parenchymal toxic edema of the liver is equivalent to acute diffuse serous hepatitis. It is interesting to note that he stressed its importance in association with the hepatic changes of thyrotoxicosis (see the foregoing material). Rössle's hypothesis is that in the presence of thyrotoxicosis a toxin is elaborated which acts particularly on the liver because of its detoxifying action.

products. Toxemia is autogenous after severe burns, the source being in the burned tissues. This acute autogenous intoxication in the first four days after a severe burn resembles greatly three other types of toxemia which physicians are beginning to understand, traumatic shock following severe injuries and the intoxications accompanying roentgen therapy or curietherapy. Observations of the physiologic-pathologic character of recent extensive burns and of the other forms of toxemia open up a new field of what might be termed diseases due to autogenous intoxication. In animals it has been found that repeated burns confer sensitization, which in turn confers a certain immunity or resistance toward burns.

Similarity to the hepatorenal syndrome is striking. There are, first, the occurrence of death with hyperpyrexia in the first few hours after the reception of the burn, corresponding to the so-called liver death and second, death as a delayed phenomenon with the clinical signs of toxemia, corresponding to the deferred death following the hepatorenal syndrome.

5. *Intestinal Obstruction.*—Simple blockage of the intestinal tract becomes increasingly important because of its secondary consequences. In clinical medicine one distinguishes the following:

A. High intestinal obstruction, clinically noted for causation of regurgitant vomiting, loss of large amounts of fluids (dehydration, anhydremia) and for disturbed physicochemical relations.

B. Low intestinal obstruction, clinically noted for causation of progressively increasing distention of the bowel and secondary vomiting.

The dangers are enormously increased because of vascular changes (strangulation ileus) and deepening toxemia. If the condition is neglected, necrotic areas form, perforation takes place and the patient dies of terminal peritonitis. There are marked differences between low and high obstruction.

The dominant characteristics of high obstruction are vomiting and loss of fluid. Physically, extreme grades of dehydration and anhydremia occur. The higher the point of obstruction and the closer its proximity to the stomach, the more rapidly depletion occurs. Chemically this has been shown (MacCallum, Vermilye, Leggett, Boas and Lintz; Hastings, Murray and Murray; Haden and Orr; Gamble and Ross; Hartmann and Smyth; Dragstedt and Ellis; Gamble and McIver, and Elman) to result in the development of a variable picture: the higher the location of the obstruction, the more rapidly the carbon dioxide content increases and the more constant and severe is the grade of alkalosis produced. Alkalosis occurs most prominently with pyloric obstructions. The lower the point of obstruction, in the upper reaches of the small intestine especially, the less constant and less severe is the alkalosis, so that often no significant change appears.

The dominant characteristics of low obstruction are distention and toxemia. The vomiting is slight or moderate, and the vomitus consists of matter from the small intestine. Azotemia is a constant finding, and in clinical practice it is my custom to estimate the gravity of the obstruction by the extent of azotemia.

In the presence of any obstruction both sets of factors are present to some extent. In many cases other recognizable factors are present. All of these can be enumerated as follows: ileus, vomiting, loss of fluids (dehydration, anhydremia), azotemia, autolysis of tissue and its effects, toxemias and preoperative or postoperative shock (and/or collapse). The picture is further complicated by the possible presence of chronic and acute cardiac disease with and without hypertension, diabetes, pneumonia or obesity.

Death occurs as a relatively sudden phenomenon with fever, oliguria, azotemia, and dehydration, or the clinical picture and the symptoms develop much more slowly. Hyperacute manifestations frequently develop with the sudden operative release of the obstruction; hyperpyrexia and toxemia are then dominant characteristics of the clinical picture, which terminates quickly in death.

The clinical similarities to the hepatorenal syndrome and to sudden death with hyperpyrexia (so-called liver death) are marked. I called attention to this similarity many years ago. In my own experience the hepatic lesions have been absent, have been immaterial or, the experiences having occurred before much interest was aroused in the hepatorenal syndrome, have not been particularly looked for or stressed.

In 1923 Rowntree and Brown made a report on a series of 11 cases of a form of toxemia which was associated with anatomic or physiologic stasis in the duodenum. The toxemia was characterized by the following rather definite clinical picture: (1) vomiting of large amounts of thin serous bile-stained fluid; (2) evidences of dehydration, a red florid complexion, a high hemoglobin value, low blood pressure and asthenia; (3) tetany-like manifestations; (4) features of superimposed uremia and (5) occasional evidences of shock. The blood showed (1) a low level of chloride, (2) a high carbon dioxide capacity and (3) a high level of urea and of creatinine. Urinalysis revealed the presence of albumin and casts. Studies of renal function showed high values for urea and creatinine and a decreased excretion of phenolsulfonphthalein. In 6 cases necropsy revealed nephrosis, with characteristic changes in the tubular epithelium, or diffuse nephritis. No hepatic lesions were described in this report.

Boyce and McFetridge expressed the belief that certain deaths in intestinal obstruction are exactly akin to such deaths after gallbladder surgery. The clinical manifestations are the same, extreme hyperpyrexia with oliguria or complete anuria if the patient happens to live

long enough; in intestinal obstruction he usually does not. If postmortem is done, there is an absence of all positive findings which could explain death, other than necrotic changes in the liver, associated with similar degenerative changes in the convoluted tubules of the kidneys if the patient has lived long enough.

Those authors explained these deaths on the basis of functional hepatic insufficiency, noted in 14 of their cases by clinical evidence, plus anatomic lesions in the liver and kidney, noted in 9 other cases. The postmortem changes were "typical."

Cole and Elman have interested themselves in this problem, and they have been able to reproduce such changes by experimental obstruction. They have proved their point by tests of hepatic function as well as by the histologic observations at necropsy.

The observations of Werelius, made in 1922, are extremely interesting. In commenting on the experimental work of Dragstedt and his associates, he pointed out that for drained and for undrained obstructed duodenal loops the results were exactly similar; but it was noted that about twenty-four hours after the loops were drained the biliary secretion stopped completely and was replaced by a clear mucoid substance or, at times, a reddish fluid. In every instance the test for bile gave negative results. The cessation of secretions of bile heralded the onset of untoward symptoms; from that time on the animal rapidly lost ground, and the fatal issue was not long delayed. Werelius drew the obvious conclusion that the stoppage of bile was of the gravest possible prognostic significance for every one of the 33 animals used. In 8 instances bile was drained directly from the gallbladder, and in the others it was drained through the duodenum. In every case stoppage of bile meant death. It is seemingly a pathognomonic prognostic sign in the presence of high intestinal obstruction.

The stoppage of bile undoubtedly indicates severe intrahepatic disturbance with possibly a complete standstill of hepatic activity—in other words, a complete hepatic insufficiency aptly termed by Werelius "ahepatism." There is no doubt that such a severe or complete hepatic insufficiency would be either the dominating cause or a most important factor in the lethal outcome.

Sudden Release of Obstruction.—Typical forms of obstruction to the outflow of the fluid content of a hollow excretory passageway are well known as regards the biliary, the urinary and the alimentary tract. During any form of toxemia of pregnancy the uterine contents act in a similar manner to the contents of the obstructed biliary, urinary or intestinal tracts, for the powerful reason that rapid emptying of the uterus relieves the abnormal condition; as such, toxemia of pregnancy becomes, also, a form of obstruction.

A curious antithesis exists in all cases of obstruction: trouble begins and develops because the obstruction is not relieved, and occasionally an

More or less sudden calculous obstruction in the urinary tract on one side is commonly followed by restrictions in the urinary secretion of the corresponding kidney up to the point of complete suppression of secretion in the given organ. In the presence of bilateral formation of stones similar disturbances of function may follow, and one considers operative release of the obstruction with concern. Usually operative release of an obstruction on one side in the presence of a bilateral lesion is followed immediately or reasonably soon by the reappearance of function up to the total normal functional capacity of the kidney at the given moment. Occasionally, however, a state of complete suppression of urine follows the operation, and the preoperative condition is suddenly intensified to the point of complete anuria: that is, all the manifestations of the obstructive state are suddenly exaggerated after release of the obstruction.

The effects of intestinal obstruction have already been discussed and are well known. Contrariwise, the operative release of intestinal obstruction is sometimes followed by exaggeration of the preceding clinical manifestations. Here, also, similar conclusions as to the relation of the release of the obstruction and the immediate exaggeration of the subjective and objective symptoms and laboratory findings are forced on one.

The phenomena surrounding toxemia of pregnancy have also been previously reviewed in this communication. With pregnancy, too, it is well known either (1) that the manifestations of the already existing toxemia may be markedly exaggerated or (2) that the patient may be precipitated into toxemia when the products of conception are rapidly

evacuated from the uterus. Again, similar conclusions in regard to the intestines are inescapable.

Interestingly and curiously enough, each variety of disturbance, with the exception of the urologic conditions, both during the stage of obstruction and subsequent to its release are symptomatically and anatomically related to the hepatorenal syndrome and/or lesions. The parallelism is exact with each variety of obstruction. Clinically one finds cases of hyperpyrexia and sudden death which recall quickly the so-called liver death and one also finds cases of delayed hepatorenal syndrome and/or lesions. All the factors which are found to occur with the latter are also present in cases of obstruction; and the cases of biliary disease do not differ in this regard from cases of intestinal obstruction or pregnancy. Degenerative changes typical of the lesions exhibited in the deferred hepatorenal syndrome are present in the hepatic cells and the convoluted tubules of the kidneys. If there is any difference, after the release of an obstruction the renal changes seem more dominant.

II. CLINICAL INCIDENCE OF THE HEPATORENAL SYNDROME AND/OR LESIONS AS RELATED TO JAUNDICE

In the previous part of this communication hepatorenal symptoms and/or lesions were discussed from the point of view of the various conditions in which jaundice is an important symptom at one time or another and in which the hepatorenal syndrome is likely to occur. It is of equally great advantage to examine the syndrome from the point of view of jaundice.

Jaundice of one form or another may occur at any stage of life, not excluding fetal existence. Patients of any age may show mild or severe forms, and it is not unusual for the mild varieties to pass over into the most severe forms under sufficiently provocative circumstances, sometimes as a slow insidious process and at other times with the dramatic suddenness of acute yellow atrophy of the liver. Extensive hepatic necrosis and concomitant renal degeneration can be found at most unexpected times, as witness the case of a stillborn boy, reported by Degener and Jaffe.

In approaching the subject from the point of view of jaundice, one notes the following groups of pathologic conditions:

1. *Essentially Surgical Conditions.*—Under this heading (previously discussed) come: (A) acute and chronic cholecystitis and cholelithiasis; (B) acute and chronic disease of the bile duct, with or without calculus formation, and (C) obstructions of the common duct.

2. *Infections.*—As long ago as 1914 Merklen differentiated a large group of "acute infective hepatorenal insufficiencies" which are caused

by simultaneous infection of both liver and kidneys. This large group of infections includes the following:

A. Bacteremia of various kinds: of the typhoid-colon bacillus type, of which the important example is typhoid fever; of the pneumococcic type, of which lobar pneumonia is the outstanding example; of the influenza type; and of the ordinary staphylococcic type.

B. Special forms of bacteremia (septicemia), of which infection by Bacterium tularense is a good example. Lee Foshay told me:

At every autopsy I have attended there have been necrotic focal lesions with necrosis in the liver, and about one-half of the cases have shown similar lesions, usually much smaller, in the kidneys. After death from tularemic septicemia there are usually countless billions of foci of necrosis throughout the entire liver substance. These lesions look just like those produced by tularemic septicemia in rodents . . . foci of necrosis are observed in the kidneys of rodents in at least one-half of the deaths, perhaps in about the same frequency as they appear in humans.

C. Local bacterial infections, usually of the typhoid-colon bacillus type, of which the outstanding example is acute cholangitis. It is interesting to note that this is possibly the mechanism whereby postoperative infections eventually progress into acute yellow atrophy of the liver.

In 1 of my own cases it was possible to demonstrate post mortem the origin, of the disturbance in an infection in the larger terminal ducts of the biliary tract.

D. Spirochetal infections, of which the best examples are spirochetosis icterohaemorrhagica and syphilis.

Fleckseder's 3 patients showed the typical symptoms of Weil's disease. The serum of 1 of the patients who recovered agglutinated Spirochaeta ictohaemorrhagiae in the titer of 1:1,000, and the symptoms included fever, severe hepatic impairment, jaundice, hemorrhagic diathesis and acute renal symptoms.

E. Undifferentiated infections by some form of "virus." It seems certain that many conditions now included in this group will eventually be classified elsewhere as soon as their cause is accurately established. For the present, this group includes some forms of so-called catarrhal jaundice (angiocholitis), especially of the epidemic variety.

3. *Various Forms of Poisoning or Intoxication.*—Under this heading (see the foregoing section) come:

A. Conditions due to pregnancy. B. Thyrotoxicosis. C. Poisoning by various anesthetic and other drugs and chemicals. These conditions have been previously discussed in this communication.

4. *Conditions in Which an Important or Predominating Pathologic Element Is Massive Destruction of Cellular Tissue.*—An outstanding example of this group is furnished by the cases of pulpification of the

liver reported by Furtwaengler and by Helwig and Orr. (See the section on disease or injury of the liver and the biliary tract and that on autolysis of tissue.)

5. *Jaundice Caused by Various Forms of Intoxication or Poisoning, in Which Hemolysis Is an Important Symptom.*—This represents a complex group, including blackwater fever and snakebite. The most characteristic form is chronic hemolytic icterus.

6. *Obscure and Undifferentiated Jaundice of Which the Cause Is Still Undetermined.*—This group includes intestinal infection and/or intoxication, of which examples are Buhl's disease and Winckel's disease.

With all these conditions both mild and severe jaundice appear. Not always is the hepatorenal syndrome to be clinically distinguished or anatomically proved. Nevertheless, from time to time the syndrome appears in association with conditions belonging to each of these groups, and in direct proportion to the frequency and extent to which the condition approaches the severe forms of hepatic degeneration and necrosis commonly grouped under the generic term of "acute yellow atrophy of the liver" the hepatorenal syndrome becomes more and more evident.

"Icterus gravis" is a general term for all forms of severe jaundice caused by degenerative, infective or autolytic changes in the liver and the kidneys. It thus includes acute necrosis of the liver, occurring as a complication of previous hepatic disease or of many of the various forms of jaundice in which the renal element seems distinctly subordinate to the hepatic lesions, and the large group of infective hepatorenal conditions in the presence of which liver and kidneys suffer concomitantly, simultaneously and equally from the same infectious cause.

7. *Acute Yellow Atrophy of the Liver.*—The ultimate state to which all the previously listed conditions may progress is acute yellow atrophy of the liver. The literature contains numerous references to the fact that at one time or another examples of this progression have occurred in association with all the conditions described.

A typical and a severe form of the hepatorenal syndrome are, almost of necessity, part and parcel of the clinical entity. At postmortem examination the extent of the degeneration and necrosis in both liver and kidney is of maximum grade. This should be expected in view of all of the facts hereinbefore outlined.

One cannot avoid the conclusion that acute yellow atrophy of the liver represents the end result of a variety of other pathologic conditions: that it may result from these various causes because of a sufficient impairment and weakening of the powers of resistance of the patient, produced by disease or by unaccustomed physiologic strain: that the lesions result from the action of poisons of various kinds: that all of these various causes produce necrotic and degenerative lesions, some-

times in the liver and sometimes in the liver and kidney, and that the degree, extent, magnitude and relative proportion of the hepatic and renal lesions, extending from those of least clinical importance to the maximum dramatic manifestations of acute yellow atrophy and hepato-renal insufficiency, are questions of the dosage of poison or toxin delivered in the neighborhood of the hepatic and renal cells.

III. INCIDENCE OF LESIONS IN THE LIVER AND KIDNEYS AND/OR OF SYMPTOMS OF THE HEPATORENAL SYNDROME AS RELATED TO ASSOCIATED AND/OR ACCOMPANYING FACTORS COMMON TO MANY OF THE HEREINBEFORE MENTIONED CONDITIONS

1. *Effect of High Temperatures per se.*—Postoperative high temperature death is not entirely new, and cases were reported and discussed in the literature by Gibson, Johnson and Brewer in 1900, by Crandon and Ehrenfried in 1912, by Moschcowitz in 1916, by Martin in 1928 and by Cutting in 1931. At the beginning such deaths (occasionally the patient recovered) were correlated with heatstroke, but in 1931 and 1934 Connell began to question the assumed relation and introduced the idea of associating hyperpyrexia death with demonstrable anatomic changes in the liver. Credit for popularization of this concept is due to Heyd. The literature now contains numerous references to the subject of high temperature or liver death.

Boyce and McFetridge called attention to the fact that in all of the conditions with which they have observed the hepatorenal syndrome the pathologic changes described as occurring in the liver and kidney were especially noted when hyperpyrexia existed. In most of their cases when the clinical course was typical the postmortem changes were also typical; necrotic changes were present in the liver and were or were not demonstrably followed by similar changes in the convoluted tubules of the kidneys, in direct proportion, as Boyce and McFetridge concluded, to the length of the interval before death. These observers suggested that similar deaths with high temperature, occurring in cases of appendicitis or kindred conditions, might well be included in this category.

For many years I have noticed that during the excessive heat of the summer months, several postoperative deaths occurred every year, the outstanding terminal manifestation being hyperpyrexia. Curiously enough, such cases have almost always been instances of disease of the liver, or the biliary tract, or of thyrotoxicosis. When I compared these cases with cases of similar involvement in which operation was performed during the winter, the fact impressed itself strongly on me, as well as on the other surgeons in the hospital, that the only differentiating

factor in the two groups was the terminal hyperpyrexia, and one could not escape the conviction that the excessive heat and humidity strongly contributed to the hyperpyrexia and the fatal outcome. Indeed, so strong is my conviction of this that during excessively hot and humid days, I, as well as many other surgeons in the hospitals with which I am connected, have stopped operating except in emergencies. Curiously enough, accidents are always to be encountered at the beginning of the "hot spells"; as soon as patients—and persons in general—have become accustomed to the heat and humidity, such deaths cease to occur, and matters return to the course to which one is accustomed in the colder periods. I have discussed this in detail because Boyce and McFetridge have not noted any increase in the number of hyperpyrexia deaths under the climatic conditions of New Orleans, and the obvious explanation is that their patients are accustomed to the heat and the humidity.

A. Pathologic Effects of Fever Therapy: Highly interesting and reliable data are now available as a result of the new fever therapy. By this form of therapy hyperpyrexia is mechanically produced by various heating machines, and extraneous factors are at a minimum and can be excluded by proper controls. Identical reactions are obtained whether fever is produced by hot baths, by use of a cabinet, by diathermy or by radiothermy; and the nonharmful (physiologic?) reactions have been summarized by Neymann and Osborne, Bierman and Fishberg and Hench, Slocumb and Popp. The temperatures produced have varied from approximately 106 to 113 F.

The report of Warren, Scott and Carpenter concerning the treatment of gonococcic infection by artificial fever in 283 cases brings out the fact that jaundice and severe nausea and vomiting developed in 15 cases. In 2 cases hematuria also appeared, continued for about one week and then disappeared, without sequelae. Such unlooked-for symptoms apparently occurred only during the warm months. In some cases the icteric index rose as high as 18 by the third day, and there was a concomitant rise in the nonprotein nitrogen content of the blood to double its normal value. The latter, however, returned to normal more quickly than the icteric index. The sugar content of the blood was usually unchanged. The chloride content of the serum remained at the lower limits of normal or dropped below, but returned to normal on administration of sodium chloride. The jaundice likewise responded favorably in from three to five days when the intake of carbohydrates as well as of saline solution was increased.

Stafford L. MacLean, of the Strong Memorial Hospital, of Rochester, N. Y., gave me the record of a case in which death followed thirty hours after a twenty-four hour fever treatment. There were definite evidences of dehydration, and he was "able to prove very

definitely that there is liver damage where the chloride has been restricted." Microscopically, "the areas of degeneration (i. e., in the liver) which suggest early necrosis appear as central in location, but the occasionally scattered peripheral involvement may indicate its extension. There are small foci of scattered polymorphonuclears in the areas mentioned." The kidneys showed "a moderate degree of cloudy swelling."

The harmful (pathologic) effects of artificially produced excessive temperature have been summarized by Hall and Wakefield, by Jacobsen and Hosoi, by Baldwin and Nelson, by Baldwin and Dondale, by Schereschewsky, by Mortimer and, most recently, by Hartman and Major. The usual autopsic observations, as summarized by Hall and Wakefield and by Hartman and Major, include: ventricles in systole; generalized venous congestion, most marked in the mucous membranes, the lungs and the liver; hemorrhage; degeneration, and cloudy swelling of the kidneys. Characteristic degeneration was described in the adrenal glands. In the 2 cases described by Hartman and Major "acute parenchymatous degeneration of liver and kidneys" was specifically mentioned. The parenchymatous degeneration in the livers of the experimental animals used by Baldwin and Nelson was situated in the peripheral portion of the lobule. According to Hartman and Major, the hemorrhages in the various organs are partially due to the administration of morphine and/or amytal.

B. Pathologic Effects of Heatstroke (Heat Exhaustion, Insolation, Sunstroke, Thermic Fever): Factual knowledge concerning the pathologic effects of fever therapy is corroborated by the effect of excessive atmospheric heat. It seems that various clinical pictures may appear, which commonly merge into one another in the same subject. The pathologic picture is bound up with the degree of external heat and the humidity of the atmosphere and with the factors of production and elimination of heat by the human body; the most important of these as regards the production of serious effects is the degree of atmospheric humidity; to a much less degree the lack of circulation of the atmospheric air is contributory.

According to McKenzie and LeCount, the most important post-morten pathologic observations include petechial hemorrhages of the mucous membranes and the skin; generalized passive hyperemia; edema of the various parenchymatous organs; hyperplasia of the spleen; cloudy swelling of the liver, the kidneys and the myocardium, and diminution of the yellow cortical material in the adrenal glands. According to Halliburton and Mott, the physicochemical mechanism of death from the hyperpyrexia of heat stroke is the coagulation of cellular globulin. This is the essential physical change which produces the cloudy swelling in the liver and kidneys.

2. *Effect of the Various Forms of Anesthesia.*—For all patients operated on, the factor of anesthesia has always entered into the problem. The effect of the anesthetic depends on the kind and quantity of the agent employed and on the extent of hepatic damage that may be already present. Gagliardi's studies on the function of the liver by means of the bengal rose test and by estimations of the degree of bilirubinemia show that in a patient with a normal liver anesthesia and surgical trauma induce a transient hepatic insufficiency, which is more or less intense depending on the type of anesthesia and on the nature of the operation. In patients with preexisting latent or demonstrated insufficiency of the liver the condition is aggravated by the anesthesia and the surgical trauma.

Stander has shown, in animals, the effect of anesthesia on the constituents of the blood and on the histologic composition of the different organs. The effects on constituents of the blood were similar for the various inhalation anesthetics and were as follows:

A. Lowering of the carbon dioxide–combining power.

B. Hyperglycemia.

C. Increase in lactic acid.

D. Slight increase in uric acid.

E. Slight increase in inorganic phosphorus.

F. No disturbance or little disturbance of the nonprotein and the urea nitrogen.

According to Stander, this blood picture is almost identical with that observed in association with eclampsia, and the anesthetics produce pronounced hepatic lesions as well as changes in the kidneys.

The work of Rosenthal, Bourne and others, chiefly with dye tests, has shown that ether causes a definite although transitory impairment of hepatic function, rarely lasting longer than twenty-four hours, while Colunumal and Ascoli, Kehr, von Haberer and Stahler, Wilensky and others have pointed out that the presence of biliary disease, particularly when there is associated jaundice, hepatic and renal damage already exists and cannot fail to be intensified by the trauma of the anesthetic.

Ether, chloroform, nitrogen monoxide, gas and oxygen and in later years cyclopropane and ethylene have been used; in many cases the operations have been done with the use of spinal anesthesia either alone or fortified by one or more of the aforementioned drugs; in a few (Boyce and McFetridge) splanchnic anesthesia was used. The hepatorenal syndrome has apparently developed irrespective of the form of anesthesia or analgesia used or of the individual drug or combination of anesthetics employed. In a very few of my own cases anesthesia by local infiltration of the abdominal wall with 2 per cent procaine hydrochloride has been employed. In the experience of Walters and

Parham, the difference in reaction between general and local anesthesia has been a difference of degree only; if the urea content of the blood is taken as a criterion, it is established that in the cases in which disturbances occurred local anesthesia combined with administration of small quantities of ether was followed less frequently by disturbances of nitrogen metabolism.[2]

3. *Effect of Anoxemia; Anoxia.*—During experiments with general anesthesia and with eclamptic states, the idea suggested itself to Stander that one had to deal, perhaps, with varying degrees of asphyxia. According to Stander, anoxemia produces acidosis, as is evidenced by a lowering of the carbon dioxide–combining power, by hyperglycemia and by accumulation of lactic acid in the blood stream. It also produces marked degeneration and necrosis of cells in all parts of the lobule of the liver as well as slighter changes in the convoluted tubules of the kidney. These changes are not associated with the deposition of fat but appear to consist in simple necrosis of cells.

Hartman pointed out that when he compared his anatomic observations in the cases in which fever therapy was used and the patient died with those of Courville in his studies of asphyxia (or anoxia), he found a striking parallelism; he came to the conclusion that asphyxia must be one of the causative factors in the harmful effects of fever therapy. He found that after the production of high temperatures in animals severe asphyxia (anoxia) was shown by the decreased oxygen saturation of the arterial blood and the low oxygen content of the venous blood, and that when the saturation fell below 65 volumes per cent the animals died.

Moon has seen similar pathologic changes in animals and in human beings as a result of shocklike states produced artificially or occurring clinically. According to Hartman, the pathologic changes produced by high temperatures are similar to those of anoxia produced by prolonged asphyxia, by carbon monoxide poisoning and by acute alcoholism. The work of Hartman and Courville is in accord with such a conclusion, in that the pathologic changes are more pronounced the longer the patient lives after asphyxia has been established.

4. *Effect of Shock and Shocklike States.*—Shock (including the term collapse) is a generic term for a series of phenomena of similar nature which are found to be caused by, to follow or to be associated with a variety of preceding events. The symptoms of shock are well known. In all forms of shock one recognizes (1) an immediate form (primary shock) of varying degrees of intensity, frequently so severe as to cause death immediately or quickly, and (2) a delayed form (secon-

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2. Compare this section with that on drugs and chemicals.

dary shock) which develops more leisurely in the first forty-eight to seventy-two hours after the appearance of the cause. This is a purely clinical differentiation.

Primary shock may be described as sudden great circulatory collapse, usually associated with loss of consciousness. It is often caused by a stunning blow or a serious disturbance of the central nervous system and may be likened to syncope or collapse. Secondary shock is characterized by low arterial blood pressure, by a rapid and thready pulse, by shallow, rapid or irregular respirations, by general restlessness and insatiable thirst, by coldness and often pulselessness of the extremities and by other evidences of circulatory disturbance. Unlike primary shock it is usually associated with a relatively clear mental state. It follows moderate or severe injuries, particularly those involving a good deal of muscular tissue and causing repeated small or severe hemorrhages.

The following forms of shock can be distinguished clinically:

A. Neurogenic Shock: Shock can be a psychic phenomenon, and as such, as far as present knowledge goes, it lies entirely outside the scope of this discussion. The sudden and frequently overpowering shock which follows a severe injury (physical, chemical or thermal) results from an overpowering stimulation of important nerve trunks, the spinal axis or the brain, and the mechanism undoubtedly varies from that of a simple or extraordinary reflex to that of a more or less complete paralysis of important nerve centers. Other factors commonly enter into the mechanism, especially the action of toxic bodies absorbed from injured tissue. The toxic effects of laked blood and of traumatized muscular tissue on the higher centers have been demonstrated in experimental animals.

B. Traumatic Shock: This includes shock produced by or following operation. It follows excessive trauma (traffic accidents or gunshot wounds) in which important or large areas of the body are affected to the point of pulpification or separation from the rest of the body and severe or prolonged operations (extensive intestinal procedures, important amputations of the limbs or radical amputations of the breast). The important element in traumatic shock is the absorption of toxic bodies from the injured and destroyed areas, and in this regard the mechanism seems related to that producing the effects of autolysis of tissue. As secondary contributing causes, neurogenic factors, hemorrhage and hemolysis enter into the mechanism of traumatic shock.

C. Shock Following Hemorrhage: All forms of shock are aggravated and intensified or caused by loss of blood. This is a mechanical phenomenon associated with the sudden marked diminution of the fluid content of the circulatory system and the tissues. When shock is due

entirely to hemorrhage, and the basic disturbance has not progressed too far, immediate relief is obtained by restoring the fluid content with dextrose and saline solutions, with acacia or, best of all, with whole blood. The mechanism is related to that of anhydremia and diminished volume of blood.

D. Hemolytic Shock: Hemolytic shock, which is dangerous, may follow blood transfusion if the blood groups of the donor and the recipient do not agree. Bogomolatz, Bajdasaroo, Vlados and others did not recognize hemolytic shock as a distinct entity but classified all complications following blood transfusion as colloidoclasia.

Hesse differentiated three forms of hemolytic shock. The first is acute, with mild vascular and cardiac phenomena which soon disappear. In this form about 50 cc. of hemolyzed blood can be taken care of by the reticuloendothelial system. The second is acute and severe, with a serious fall in the blood pressure. In 4 of Hesse's cases of this type death occurred within an hour and in 24 cases within a few hours. In some cases the chief sign was increased intestinal peristalsis. The third form of hemolytic shock described by Hesse is a delayed form, of which the first signs appear after periods varying from twelve to twenty-four hours. This form is infrequent.

The anatomic changes following hemolytic shock are most interesting: In Malijšev's patients and experimental animals there were the usual signs of hemolysis. In addition, when death was delayed for any length of time there were degeneration of the epithelium of the renal tubules and necrosis in the centers of the hepatic lobules. According to Malijšev, Skundina and Elanskij, such changes are not to be attributed to mechanical obstruction alone but rather to the anemic condition of the organs, the spasm of the capillaries and the toxic action of the products of decomposition of hemoglobin.

Hesse and his school subdivided the mechanism of hemolytic shock into four parts: (1) nonspecific protein reactions of varying intensity; (2) hemolytic shock and its sequelae; (3) intoxication of the organism by denatured proteins occurring in preserved blood, and (4) anaphylaxis. Petroff and Iljin have shown that the toxic effect of heterogenous blood is related to its protein content. The introduction of either erythrocytes or plasma into the blood stream of experimental animals is followed by especially marked toxic effect and the toxic substances are similar to the complicated protein components of adenosin phosphoric acid.

E. Peritonitic Shock: Peritonitic shock, according to König, has a characteristic picture—a circulatory change, with dilatation of the capillaries and injury to their walls, which is followed by transudation. Holzbach added another factor by attributing the changes in the walls

of the vessels to toxic action. In the presence of peritonitis the blood gathers in the splanchnic area, particularly in the intestines and in the liver. In all forms of peritonitis infection is an important factor. In biliary peritonitis the toxic effect of extravasated bile is an added factor.

F. Shock Associated with Acute Intestinal Obstruction: The probable cause of the shock syndrome following intestinal obstruction is intoxication with histamine, with other products of injured and necrotic tissue and by absorption of bacteria and their products from the obstructed bowel.

G. Anaphylactic Shock: Occasionally, especially in experimental work, there are marked resemblances to the phenomena of anaphylaxis. In some cases the sensitization seems of major importance; in others anaphylaxis plays a minor role. In any case the anaphylactic manifestations seem always to be associated with the manifestations of other mechanisms.

H. Shock Produced by Action of Toxin: Nussbaum was the first to correlate the action of toxins with the production of shock. Experimental work has centered largely around shocklike states produced by trauma and hemorrhage. In animal experiments shock produced by traumatizing a limb does not appear until the tourniquet is removed from the limb; and during the World War an English research committee found that traumatic shock did not occur in the dog if the vessels of the extremity were clamped before the injury was inflicted. König showed that if injured muscle cells are macerated quickly enough, a substance is formed which in small doses is fatal to animals. Cannon, Sierra and Lemon and Schoercher suggested that this substance is histamine, and in experimental work histamine regularly produces a shocklike state. Similar toxins are elaborated from the platelets and from defibrinated blood. Zipf was able to demonstrate that these toxins are the nucleotides, especially adenylic acid and adenosin. Curiously enough, adenylic acid is found in the fluid secretion of the blebs caused by burns.

According to other investigators (Pannella), shock is an anaphylactic state caused by absorption of albuminous material from the destroyed tissues. It has also been pointed out that the toxic action of acetylcholine and carnosine (substances which are not foreign to the body) on the vascular system, in conjunction with the vascular dilatation resulting from neurogenic reflex action which causes irritation of the sympathetic and sensory nerves, would be entirely sufficient to explain the clinical phenomena of shock.

I. Shock Produced by Chemicals: In experimental work a number of chemicals and drugs have been used in the production of shocklike

states: these include germanin (König; Doelle), heparin (Keyes and Strauser; Doelle) and novirudin (sodium combined with humic acid) (Doelle). The experiments brought out the fact that the shocklike state does not occur when the blood is incoagulable; von Falkenhausen had shown this also for anaphylactic shock and Friedberger for peptone shock. The experiments showed that germanin, arsphenamine and heparin destroy the complement-forming and thrombotic properties of the blood. In this regard it is interesting to compare the clinical use of germanin in the treatment of pemphigus (see the section on the action of drugs and chemicals). The important point of all of this experimental work is that a shocklike state cannot be experimentally produced when the blood is incoagulable.

The process is seen in an exaggerated form in hemolytic shock after the transfusion of blood of an unlike group. Sudden hemolysis takes place as the result of liberation of the prothrombin (using up of the complement) from the antiprothrombin-prothrombin complex. Finally, Krehl concluded that the process is probably related to the endothelial cells, the liver or the bone marrow. König concluded that the liver plays a particular role as a depot organ and is the chief site of the formation of antithrombin (heparin). This is indicated by the enlargement of the liver, the central hepatic softening and the outpouring of glycogen in shock.

No one theory will explain all of the phenomena observed in shock. Many of the numerous factors involved—depression of the vital centers, anhydremia (loss of blood volume), dehydration, anoxemia (anoxia), acidosis and experimental factors in artificial shocklike states—have been reviewed in this communication, and the interrelations and similarities of the demonstrable anatomic lesions can be easily grasped from the factual presentation. It is evident that in many shocklike states typical changes have been demonstrated in the liver and kidneys. It is also evident that shock or a shocklike state is a complicated condition which can be produced by many agencies, including reflex or neurogenic action, trauma or disintegration of tissue. So many are the associated factors and so intimate are the associations of these with each other and with their provocative causes that it is difficult to say to which ultimate radical the hepatorenal symptoms and/or lesions should be, ascribed.

5. *Effect of Dehydration and Anhydremia.*—Generally speaking, the daily normal loss of water, according to Maddock and Coller, includes from 800 to 3,000 cc. as urine, approximately 200 cc. in the stool and an insensible loss (by cutaneous evaporation) of from 1,000 to 1,500 cc. The maintenance of the electrolyte balance requires a daily supply of

approximately 5 to 6 Gm. of sodium chloride. In normal health the variations in these approximate figures are slight.

In abnormal conditions, even those of most transitory nature, the loss of water is increased because of vomiting, diarrhea and excessive sweating and because of ingestion of substances which normally increase, through their diuretic effect, the secretion of urine. In long-standing illnesses the amount of water lost per diem is increased, and the increase depends on the nature of the illness, on the presence of fever and on the importance of diarrhea and/or vomiting.

Various degrees of dehydration occur under the following clinical conditions:

A. In pediatric practice the effect of loss of fluid from the body in the first few days of extrauterine life is well recognized. High grades of fever are common, and it is well known that the lost fluid must be immediately replaced if untoward results are to be avoided.

B. In surgical practice, during operations of any magnitude, the loss of fluid, according to Maddock and Coller, amounts to approximately 1,000 cc. The loss of blood also may be considerable. The importance of replacing this lost fluid in order to alleviate the symptoms in the immediate postoperative interval or to avoid any further consequences is so well known that the practice of introducing fluid into the body has become a routine in almost every well regulated hospital.

C. As has been indicated elsewhere in this communication, similar losses of fluid, amounting under experimental conditions to between 20 and 30 per cent of the blood volume of the body, are known to occur as a concomitant phenomenon of the autolysis of tissue and after destruction of portions of the body by heat.

D. Similarly, loss of fluid occurs with local and diffuse forms of peritonitis and with intestinal obstruction.

E. Finally, the effect of loss of fluid on persons lost in the desert without water is well known. Death is the inevitable result. Unfortunately, I have no data and do not know where to find any concerning the pathologic effects, either morphologic or functional, on the human body of such conditions.

Accompanying any extraordinary loss of fluid there is an increase in the concentration of the blood, as shown by an increase in the percentage of hemoglobin and in the hematocrit readings. According to Mason and Lemon, the increased concentration of blood is due to a decreased volume of plasma, a decreased volume of serum and an increased fibrin content. The concentration of the blood, as shown by the increase in the percentage of hemoglobin and in the hematocrit reading, is according to Harkins roughly proportionate to the loss of

fluid, but the blood pressure remains near normal until death approaches and then falls rapidly.

According to Stander, peptone, histamine and histamine-free albumose each produce a blood picture suggesting anhydremia. The moisture content of the blood is lowered, although the increased concentration of the blood is perhaps not wholly due to this dehydration. It may be due also to actual loss of plasma, resulting from capillary dilatation.

Mason and Lemon proposed the hypothesis that any such extraordinary loss of fluid is productive of a form of secondary shock. They have also introduced the conception that the anatomic changes associated with the hepatorenal syndrome are due to the anhydremic condition which follows. Many other factors are all too often associated with the primary illness or with the operation which commonly is done. It seems difficult to correlate the anatomic changes with this one factor alone, although, as has been pointed out, it is constantly present and must be reckoned with.

6. *Effect of Autolysis of Tissue.*—Many facts of importance in relation to the hepatorenal syndrome and/or lesions are to be learned from a study of the facts and phenomena preceding and accompanying autolysis of tissue during life. Clinically this association is found under the following circumstances:

A. In cases of strangulation ileus: The effect of obstruction of the bowel has been considered. The studies of Wangensteen and Waldron showed that the autolysis of tissue accompanying strangulation ileus intensifies the effects of simple obstruction of the bowel.

B. In cases of traumatic destruction of tissues during severe injuries: This occurs with the tissues of the viscera as well as with the tissues of the superficial muscles. The incidence and other aspects of this condition as related to the liver have been discussed in a previous part of this communication.

C. In cases of necrosis of tissue occurring as an untoward and unexpected accident after surgical operations: The best example of this takes place in the liver, in which, very rarely, during operation on the gallbladder and bile ducts the main stem or an important primary branch of the hepatic artery is injured; necrosis of the appropriate segment of hepatic tissue follows. This is another variety of the condition described in the foregoing section.

D. In cases of burns: This subject has been extensively discussed elsewhere in this communication.

E. In gangrenous inflammations of the appendix and the gallbladder: Such inflammations also involve autolysis of tissue to some extent.

F. In cases of necrosis of tissue resulting from the application of radium: Many years ago I observed the following case in consultation:

The patient was a middle-aged woman in excellent condition except for carcinoma of the fundus of the uterus. An intrauterine application of radium was given by the attending physician. Within a week the woman went into toxemia of the highest grade, with extreme hyperpyrexia; slight jaundice was present. Death occurred several days later. Postmortem examination showed peritonitis, total necrosis of the uterus and degenerative changes in the liver and kidney.

G. In cases of necrosis of large bulky tumors, such as uterine fibromyoma.

H. In experimental work: A great deal of work has been done on the phenomena which follow autolysis of tissue, by Mason, Davidson, Matthew and Rastello, Wangensteen and Waldron, Haden and Orr, Ellis and Dragstedt, Delbet and Karajonopoulos, Mason and Lemon, Andrews and Hrdina, Mason and Nau and others. Usually the experiments consist of placing within the peritoneal cavity pieces of the various abdominal organs, taken from the same or another animal and separated and disconnected from all of their biologic attachments. Mann noted similar effects when, in an attempt to remove the entire liver, pieces of unattached hepatic tissue were allowed to remain within the peritoneal cavity. According to Andrews and Hrdina, similar effects are noted when the pieces of tissue are placed within the pleural cavity or beneath the skin. In almost all the experiments the animals die within from one to two days.

The studies of Wangensteen and Waldron showed that pieces of the pancreas, the liver and the intestine are the most toxic; renal tissue is relatively nontoxic, and splenic tissue is intermediate in toxicity. Intestinal, pancreatic and hepatic tissue appear to disintegrate into toxic bodies more quickly than do renal and splenic tissue. The size of the autolyzing piece of tissue is also important, as Boyce and McFetridge pointed out. The injected substances prepared from the various tissues (Andrews and Hrdina) appear to be about equally toxic, except that there seems to be an early qualitative difference in the toxicity of the autolyzing tissues, in accordance with the rapidity of disintegration and liquefaction. With transplants of hepatic tissue Mason and Nau have noticed differences in accordance with the point from which the transplants are taken.

The pathologic pictures encountered by Mason and his associates, by Wangensteen and Waldron, by Boyce and McFetridge, by Andrews and Hrdina and by others, in experimental animals presented strong similarities. The animals were found dead in from ten to eighteen hours. In such experiments the abdomen is generally distended with gas if

the animal lives more than twelve hours; between 300 and 500 cc. of blood-stained exudate is present within the peritoneal cavity, and gas is present in the exudate and on the surface of the liver and of the other viscera. Generally deposits of fibrin and of frank pus are comparatively rare. The entire peritoneal surface is intensely inflamed and hemorrhagic. The hemorrhages occur also in the other endothelial surfaces of the body, especially the pleura, and in the lung.

The most striking changes occur in the host's liver. It is infiltrated with gas, and far advanced degeneration and necrosis are scattered throughout. There is minimal infiltration with leukocytes.

Turley's description of the microscopic pictures in the liver and kidney, as given by Mason and Nau, is as follows:

Cords of central and middle zones of the lobules [of the liver] show rarefaction so marked that the nuclei of the cells appear to be held in place by a lace-like web. The cells of the peripheral zones have a fine, foamy appearance. The tissues of the portal canals are infiltrated with lymphocytes, endothelial cells, and an occasional polymorphonuclear leucocyte. This infiltration is most marked around the bile ducts. The liver is the victim of what appears to be a rather acute and marked fatty degeneration plus a septic cholangeitis.

The lesions in the kidney vary with the different fields. In some fields the capillaries of the tufts and tubules are engorged with red blood cells, the tufts are swollen until they fill the subcapsular spaces, the tubule epithelium is swollen, and the inner margins are frayed. The lumen contains granular débris. In other fields the glomerular tufts are approximately normal in size, leaving a fair subcapsular space. The tubular epithelium shows some erosion, but also many of the cells show the brush-like inner border. This kidney appears to be recovering from a rather intense, toxic parenchymatous nephritis. The cause of the condition is still operating though in lessened intensity as is shown by the areas of present, acute nephritis.

Andrews and Hrdina emphasized the fact that

It was almost impossible to distinguish between the appearance of the transplanted liver and the host's liver. Both showed almost equally severe autolytic changes. On microscopic examination, while the transplanted liver showed more advanced necrosis, the host's liver showed such changes that one could not be sure without reading the labels on the slides which was which.

Boyce and McFetridge have criticized the interpretation of the microscopic pictures stressed by Andrews and Hrdina, on the ground that they have seen such pictures only when postmortem examination was delayed. It is true that production of gas continues after death, and the greasy appearance or feel of the liver might be a postmortem effect. Nevertheless, it is difficult to associate infiltration by lymphocytes, leukocytes and endothelial cells and the appearance usually associated with cholangitis with anything except biologic changes, which can occur only during life.

A minority of observers (Dragstedt) have not been convinced that toxemia can result from autolysis in the absence of bacterial growth; they have concluded that the dominating factor is the growth of bacteria in the liquefying tissue.

The bulk of the experimental evidence, however, shows that death which occurs under conditions of autolysis is not produced primarily by infection; the customary presence of the gas-producing Welch bacillus indicates a concomitant, contributory, catalyst-like and synergistically intensifying factor in the fatal outcome. Rather does it seem that death is primarily due to a toxemia of maximum grade. The evidence shows that the toxin is produced in the process of autolysis of the implanted tissue in the experimental animal or the destroyed and/or necrotic tissue in the human being. According to Andrews and Hrdina, the toxic agent is a water-soluble thermostable body which is precipitable by alcohol or chloroform, stains purple in solution when the biuret test is used, is with difficulty dialyzable and probably falls within the albumose group. In support of this opinion, Andrews and his co-workers have cited the fact that the anaerobic bacilli recoverable from experimental animals after death are not toxic when injected intraperitoneally or intravenously. Boyce and McFetridge expressed agreement with this opinion.

7. Effect of Acute Peritonitis.—Acute peritonitis occurs as a complication of many of the conditions described in this communication—trauma, infections and all types of abdominal operations. The role of peritonitis is, then, commonly secondary. Whatever symptoms are present in the liver and kidney should be referred to the primary condition when peritonitis is secondary or metastatic. In addition, in this form as well as when the peritonitis is primary and results from trauma, associated factors (neurogenic factors, shock, collapse, dehydration and toxemia) develop; the role and importance of the latter in the pathogenesis of hepatorenal lesions and/or symptoms have been previously outlined in this communication.

Biliary peritonitis has been observed by Touroff in a small series of cases in which the hepatorenal syndrome was present, and he has suggested that the biliary peritonitis is the cause of the syndrome. This has not been corroborated in other clinics. In addition, as can be seen from the factual presentation in this communication, there are many other factors to consider, and biliary peritonitis cannot be considered a possible cause in many of the cases recorded in the literature.

In all cases of peritonitis the factor of infection dominates the picture, and in spite of many associated conditions, whatever hepatic and/or renal changes occur are probably directly due to this factor more than to any other.

IV. EXPERIMENTAL PRODUCTION OF LESIONS IN THE LIVER AND KIDNEYS

Experimental investigations have attempted to produce in animals hepatorenal lesions acceptably similar to those observed in human beings, but have not generally succeeded. In general, the investigations have followed the following trends:

1. *Traumatic Destruction of Parts of the Liver.*—Helwig and Schutz and Boyce and McFetridge have worked along these lines. The results have not been altogether satisfactory. Nevertheless, the clinical experiences previously referred to in this communication regarding clinically observed pulpification of the liver cannot be dismissed. Some of the experiments in autolysis of liver and of tissue lend considerable weight to these investigations.

2. *Interference with Hepatic and Portal Circulation.*—Investigations of this nature have been made and reported by Ravdin, Behrend, Boyce, Lampert and McFetridge, Helwig and Schutz, Helwig, Schutz and Kuhn and others. These experiments have given no positive evidence regarding hepatorenal lesions. In one experiment made by Gundermann, however, uremia followed ligation of the hepatic artery. In other experiments Gundermann tied the left portal vein; atrophy of two thirds of the liver developed; oliguria followed, with albuminuria, and casts and red blood cells appeared in the urine. The latter experiment probably had more relation to the experimental production of cirrhotic conditions of the liver.

3. *Obstruction of the Biliary Tree.*—This procedure has been successful in reproducing hepatorenal lesions in animals, especially when the obstruction was later suddenly removed. Most of this work was done by Boyce and McFetridge.

4. *Injection of Extracts of Damaged Liver.*—Attempts have been made to reproduce hepatorenal lesions by the injection of extracts of the livers of animals in which hepatic damage had previously been produced by:

A. Obstruction of the biliary tract, with and without subsequent sudden release of the obstruction.

B. Injection of various chemicals.

C. Disease and/or operation (as in a case of "liver death").

The experiments were made by Boyce and McFetridge, who obtained positive results only with the extract from the animal who had suffered "liver death." They pointed out that only saline solution or watery extracts give positive results and explained the failures on the basis of that fact, and of the probable insufficiency of dose or concentration of the causative agents in other experiments.

5. *Implantation or Injection of Normal Liver and/or an Extract of Normal Liver.*—This was done in the course of experiments on autolysis of tissue by Mason and associates, Dragstedt and his co-workers, Andrews and Hrdina and Boyce and McFetridge. The experiments failed to produce either a clinical picture or lesions which in the opinion of the experimenters were similar to those observed clinically.

In contradistinction to these experimental results, Pytel stated that he was able to reproduce the hepatorenal syndrome in rabbits by ligation of the hepatic artery, by subcapsular traumatization of the liver, by intraperitoneal and intravenous injection of extracts from the livers of animals in which the syndrome was produced and by injection of blood from such animals into normal animals.

COMMENT

PHYSIOLOGIC, COMPLEMENTARY AND CLINICAL ASSOCIATIONS OF LIVER AND KIDNEY

The close association of the liver and the kidney in the performance of certain metabolic processes dealing with detoxification of various substances by the former and their excretion by the latter suggests definite interdependence.

The literature dealing with more obscure relations between the kidneys and the liver has been fully reviewed by Lieber and Stewart, Henschen and Rosenbaum, and other recent investigators (Mayer, Sacchetto and Oselladore, Bompiani and Koch) have pointed out the association of certain individual lesions occurring in these organs. According to Stäheli, Dourmashkin and Fitz-Hugh, operative manipulation of the extraparenchymatous conducting system of either the liver or the kidney may result in reflex suppression of the functional activity of the other organ. In addition, clinical (Porges and Grossman) and experimental (Asher, Meier and Mosonyi and Voith) observations, including the results of administration of liver extracts to animals (Lampe, Glaubach and Molitor) suggest that the regulatory mechanism of renal function originates in the liver. Similar evidence is supplied by the work of Gundermann; Haberer; Narath; Mann; Dicker and Andersen; Allan, Bowie, McLeod and Robinson, and Whipple and Speed.

Pytel called attention to the complementary nature of lesions of the liver and the kidneys. In most of the reported cases a secondary renal effect or impairment developed after primary disease or traumatic impairment of the liver; in a lesser number a primary renal lesion was followed by hepatic manifestations.

Dourmashkin's report, made in 1928, described 2 cases of coexisting urethral stricture and hepatic cirrhosis. A few hours after sounding of the urethra of the patients a chill and high fever occurred; drowsiness followed; recurrence of

previously existing jaundice was then noticed and deepened rapidly; a typical cholemic picture finally developed, and the patient died. The course of the second patient was similar.

Dourmashkin's report undoubtedly stimulated the report of Fitz-Hugh along similar lines. The latter author described typical hepatorenal syndrome with liver-to-kidney progression in 1 of his cases, while the next case reported by him was one of primary urologic disease, in which instrumentation was followed by chills, fever and other urologic symptoms indicative of infection and one week later by jaundice and other clinical and laboratory evidences of hepatic involvement.

There is no doubt that the mechanism of transfer in such cases operates through infection; nevertheless, the complementary effect is well illustrated in these reports. In Dourmashkin's cases no drug was used which could possibly, in urologic involvement, have produced the hepatic symptoms and lesions and the terminal cholemia. In Fitz-Hugh's cases some form of local anesthesia was employed, and all of the patients had a background of previous use of drugs (alcohol, arsphenamine and other substances) which might have predisposed to hepatic damage. In Pytel's opinion these observations indicate a strong functional hepatorenal relation.

PHYLOGENETIC RELATIONS OF LIVER AND KIDNEY

According to Lieber and Stewart, The existence of a phylogenetic relationship has been demonstrated in fishes, amphibians, reptiles and other lower vertebrates and, according to Roger and Spanner, in birds in which both the liver and the kidneys possess afferent portal veins. In mammals the kidneys have a portal venous supply in early embryonic life (Spanner), and although this tends to undergo involution there are indications that vestiges of it may persist and become functionally active in adults under certain conditions. Hemorrhages in the renal cortex, regressive changes in the epithelium of the renal tubules and the development of large, finger-like anastomoses between branches of the renal and portal veins have been encountered both in animals (Claude Bernard, Villaret, Tuffier and Léjars and Villaret and Justin-Bezancon) and in human beings with increased portal pressure (Léjars, Giacomini, Henle, Virchow and Hyrtl). According to Rosenbaum, this vascular mechanism may be responsible in part for the occurrence of renal changes follow-ing extensive damage to the liver, some of the blood from the portal vein being carried directly to the kidney by way of the ordinarily unused collateral blood channels.

There is no doubt that some of the vagaries of the quantitative or qualitative distribution of hepatic and renal lesions are at least partially accounted for by the existence of the separate vascular circulations through the liver and kidneys. It is possible and probable that at certain times and from certain areas (for instance, the mesenteric area) material is always passed primarily through the liver, whereas at other times and from other areas (for instance, the general circulation, as in chemical poisoning, or the lower portion of the intestine), material is passed directly into the vena cava and, without the intervention of the

liver, directly through the kidneys. Under the latter circumstances hepatic lesions and manifestations may be at a minimum or entirely absent, and the renal lesions and phenomena may be dominant and at a maximum.

DISTRIBUTION OF SIMILAR DEGENERATIVE LESIONS IN OTHER PARENCHYMATOUS ORGANS

In addition to the anatomic, functional and phylogenetic relations between the liver and the kidneys, the association of symptoms and/or lesions of the liver and kidneys is further complicated because of the fact that in postmortem protocols similar degenerative changes are sometimes noted as having occurred in the brain, the adrenal glands and other parenchymatous organs (Wilson; Bardeen; Weiskotten). Postmortem changes are also well known, and their mere mention should indicate the necessity for, and the occasional difficulty of, their proper integration.

GENERAL SIMILARITY OF LESIONS

On the basis of the observations made in the present study, no sharp differentiation can be made between the lesions occurring in association with primary pathologic conditions of the liver and biliary tract and those found in association with any of the other diverse conditions described. Although the former may appear to be somewhat more marked, the apparent preponderance may be discounted to some extent because, first, the hepatorenal syndrome does not develop sometimes when one has every reason to expect it; and second, the extreme variability of human pathologic material and the difficulty of evaluating the influence of variable and uncontrollable factors render it impossible to attribute much importance to such quantitative or even qualitative differences.

OCCURRENCE OF HEPATIC AND/OR RENAL LESIONS CLINICALLY

It must be emphasized that the hepatorenal syndrome does not always develop under the same conditions. It is sometimes difficult also to reconcile any particular manifestation or factor with the general mechanism and pathologic picture involved in the biologic concept. All this is baffling. A number of explanations, however, appear:

1. There is no doubt that in this, as well as in other medical matters, the appearance or nonappearance of the symptoms and/or lesions bears an important relation to the severity of the primary cause, to dosage if the condition is caused by a drug, or to the extent and severity of the preceding state. A good example exists in the manifestation of jaundice. For instance, it is difficult to explain, except on a quantitative basis, the presence or absence of jaundice in cases in which the hepato-

renal syndrome is traumatically produced. It may depend on the amount of hepatic tissue destroyed. On the other hand, the jaundice may be brought about purely mechanically, by obstruction of a sufficient number of the larger ducts by pulpified hepatic tissue, by secondary swelling of the tissues surrounding the duct walls and of the duct walls themselves or by both of these mechanisms. This seemed to be an important element in Helwig and Orr's case, the report of which said that "the pulpified liver tissue . . . was so located as to include the larger proximal ramifications of the right and left hepatic ducts." A possible aid in arriving at the mechanism of the jaundice in Helwig and Orr's case, which might be furnished by study of the qualitative variations of the van den Bergh test, is not available in the protocol furnished by these observers.

2. An important suggestion, made by Rabinowitz, that sensitization of the liver to protein (whether by surgical trauma, inhalation, ingestion or parenteral injection), opportunity for which is sufficiently abundant in everyday life, renders the liver increasingly susceptible to the toxic damage may help to explain the reason why some patients go through a rather fulminating course to death while others show mild symptoms and eventually recover or possibly show no symptoms at all. The sensitization which occurs after repeated burns has been mentioned specifically by Duval.

3. There is no doubt that in many cases more than one factor is operative in producing the hepatorenal disturbance. The resultant action is cumulative or synergistic in the cases in which the hepatorenal syndrome appears and is sufficiently powerful to cause the symptoms or lesions in the liver and/or the kidney.

4. The amount of compensatory effort in any parenchymatous organ is, as is well known, large; and nowhere is this effort greater than in the liver and kidney. It cannot be otherwise than that this factor of safety plays an important part in determining the manifestations of disease in these two organs. This also bears an important relation to the powers of resistance of any person.

NONSPECIFICITY OF HEPATORENAL LESIONS AND/OR SYMPTOMS

In contradistinction to the opinions of Helwig, Schutz, Kuhn and Orr and Boyce and McFetridge, none of the observed facts will permit one to assume any specificity of mechanism or pathogenesis in the production of the hepatorenal lesions. Abundant experience has shown that hepatic necrosis occurs under a variety of clinical conditions. Even the complicating states and factors previously discussed in this communication are found in a variety of other clinical conditions, and

there is no convincing proof that they are specifically bound to the hepatorenal lesions.

It is not correct to ascribe any specific nature or character to any hepatic cell toxin or to its action on the kidney. Any toxin developed in the hepatic cell because of its degeneration is biologically a tissue toxin, which, surely, is similar to the tissue toxins developed in the course of degeneration of other cells, such as occurs, for instance, after burns of the skin or traumatic destruction of muscles. Finally, many renal manifestations occur also under circumstances far removed from those under discussion.

SIMILARITY OF EFFECT PRODUCED BY A VARIETY OF CAUSES

In any consideration of the causative factors associated with the hepatorenal syndrome it should be noted that a similar effect may be produced by a variety of causes. Good examples are afforded by superficial burns, traumatic destruction of the superficial musculature and autolytic necrosis of parenchymatous organs. In each of these, destruction of cells and undoubted changes in intercellular tissues occur because of the application of heat, because of the physical destruction of normal relations and structure and because of chemical (and/or bacterial) action. Profound and excessive neural stimulation and hemorrhage are present in two and local loss of fluid in all three. The end result is, nevertheless, the same whatever the cause and encompasses a change in chemical and morphologic structure and the production of a state clinically recognized as shock.

ASSOCIATED GENERAL CONSTITUTIONAL OR OTHER FACTORS COMPLICATING HEPATORENAL LESIONS

Many patients whose illnesses are of interest in the present discussion were above the age of 40, and many of them, in addition, were afflicted with certain conditions—undernutrition, obesity, diabetes, hypertension, cardiac disease or nephritis—which commonly appear when a person passes 40. Postmortem protocols on such persons commonly lay bare various degenerative lesions—fatty degeneration, vacuolar degeneration or pressure necrosis in passive venous congestion—which physicians have come to associate pathogenetically with age, with the normal wear and tear of tissue, with the effects of the aforementioned abnormal states and possibly with other obscure factors.

HYPERACUTE, HYPERPYREXIC FORM—SO-CALLED LIVER DEATH

It has been said that the manifestations in cases of hyperpyrexia death (so-called liver death) are more or less similar to those in cases of delayed hepatorenal syndrome, and to a certain extent this is true.

Many clinical symptom complexes, however, have such general similarities. It has repeatedly been claimed that the differences in the character and extent of the pathologic lesions demonstrable in these two groups are only quantitative and depend on the length of time the patient lives after the inception of the biologic process. The latter statement, it seems to me, begs the question to a certain extent, as there is no completely indubitable evidence that the time element is so important. In certain cases of either type no lesion of any kind is demonstrable. Nevertheless there is no doubt that it must take some time for any lesion to reach its maturity or, at least, its demonstrability.

As a matter of fact, the preceding factual résumé seems to indicate that the outstanding manifestation, namely, the hyperpyrexia, is itself capable of producing the hepatic lesions. It would be logical, therefore, to hold that the pathogenesis of the condition leading to hyperpyrexia death is independent of the hepatic lesion and that the entire manifestation and the usual fatality are due to something else. Up to the present time no conclusive evidence has refuted this opinion. There are other medical and surgical situations, notably the crises in cases of thyrotoxicosis, in which a similar symptom complex follows disease and operation and in which hepatic changes and lesions are known to be secondary to the thyroid disturbances, which bolster up this point of view strongly.

There is no doubt that the dramatic intensity and fulminant development of the symptoms in cases of hyperpyrexia could be due to an overwhelming bacterial infection, as witness conditions occurring after any number of other types of operation in parts of the body widely removed from the liver and under widely different circumstances, in which it is known that the similar clinical course is due to infection and to infection alone.

In any case the impetuousness of the hyperacute form is related to the size of the dose of the causative agent; to the presence or absence of any associated allergic mechanism; to the symbiotic action of any mixed bacterial infection; to the synergistic action of associated causes and to the suddenness of the force which produces or sets in motion the pathologic changes. The abruptness of action necessarily produces an overpowering effect and becomes a compelling agency in the generation of functional and anatomic changes. There is no opportunity for adequate preparation and counteraction, as there is in cases in which the compelling factors develop slowly. This factor has special force in the cases of rapid death with hyperpyrexia, as well as special application in those in which the condition develops when any obstruction is released suddenly.

Many mechanisms have been involved in the sudden production of overpowering symptoms when an obstruction is suddenly released. The compelling agency has been correlated by various observers with various

states, such as anesthesia, shock, infection, absorption of toxins, dehydration and alkalosis. While the question is still not completely settled, present knowledge inclines one to the opinion that the production of symptoms is related to destruction of tissue at the site of obstruction (ulceration, gangrene) and to the greater facility thus produced for the flooding of the organism with tissue or with bacterial or possibly other obscure toxins. Possibly the newer knowledge of allergic mechanisms and hormonal action may add light to the problem, and continued investigation may bring forth neurogenic factors which may help to explain the acceleration and intensification of the pathologic mechanisms and effects.

In some of the reported cases in which hepatorenal lesions and/or symptoms appeared (compare especially the section on the effects of fever therapy) similar.degenerative lesions were found in other organs, for instance, in the brain. Should such degenerative lesions affect the centers controlling body temperature, it is not inconceivable that the hyperpyrexia encountered clinically might be a direct result of such localization.

The explanation of the mechanism of liver death cannot be lightly dismissed as a "liver effect." Too little in general is known to justify trying to explain the phenomenon of death on any such basis. It is true that in the sense that hepatic function is intimately bound up with the phenomena of life its cessation is just as intimately one of the phenomena of death. All this, however, is philosophy and not medicine.

RELATION OF THE HYPERACUTE HYPERPYREXIC FORM (SO–CALLED
LIVER DEATH) TO THE DELAYED CLINICAL AND PATHOLOGIC
MANIFESTATIONS IN THE SO-CALLED HEPATO-
RENAL SYNDROME

There seem to be two types of hyperpyrexia death. In one the clinical manifestations and hyperpyrexia are demonstrably unaccompanied by anatomic changes in the liver and kidney. Clinically, the picture is that of hyperacute infection, and it seems to me that it should be excluded from the general category of hepatorenal syndrome. In disease of the biliary tract following operation the manifestations of hyperacute infection have not, in my own experience and in that of many other clinical observers, been accompanied with the characteristic hepatic and renal changes, have commonly been associated with other competent causes of the symptoms and pathologic conditions and have impressed me strongly as evidence of overwhelming bacterial infection. I believe that this type should be classed not with the hepatorenal syndrome but rather with the broad group of bacterial infection.

In the second group, with similar clinical manifestations and hyperpyrexia, anatomic lesions can be demonstrated in the liver and kidney.

These anatomic changes have been most marked when the condition was caused by trauma, and it seems to me that only such suddenly produced conditions can show any resemblance to the symptomatic and anatomic manifestations of the delayed hepatorenal syndrome. One can understand that in the case of trauma the development of the symptoms and lesions would be rapid, owing to the character of the inciting cause.

HEPATIC LESIONS

It must seem obvious from all of the preceding facts, from the domination of the liver and the protean character of its functions and biologic connections with digestion and metabolism that more than one cause or set of causes may initiate a mechanism which would produce the characteristic degeneration of hepatic cells. . In clinical practice a breakdown can occur in persons whose hepatic structure and function had previously been apparently normal, or, perhaps more probably, in persons in whom some hepatic damage had already existed. From the factual knowledge and experience previously reviewed in this communication it must be concluded that: 1. The number of apparent and/or apparently unrelated potential causes must be large and must include the following: chemical bodies, introduced from without the body or produced within the body as a normal or abnormal metabolic event and (in either case) either neutralized or not promptly excreted; bacterial infections, and tissue toxins of various origin and probably related chemical structure, produced by destroyed or degenerating tissue (as after trauma or burns). 2. It is probable that in the vast majority of cases some obscure combination of bacterial and chemical toxin is the essential provocative cause. 3. Therefore, this combination of causes can be equally operative in cases of primary hepatic disease, of thyrotoxicosis, of burns, of other primary or secondary conditions enumerated in this review, or possibly, of still other as yet unidentified and obscure conditions.

In various conditions the localization of the cellular degeneration in the hepatic lobule has varied from the center of the lobule to its periphery. This may be an accidental distribution of the action of the causative toxic body; it may depend on other circulatory changes, or it may be of no biologic importance. The essential fact is that degeneration of hepatic cells occurs in many clinical conditions and can be reproduced, under certain conditions, in some experiments on animals.

RELATION OF THE HEPATORENAL SYNDROME TO DISEASE OF THE LIVER AND THE BILIARY TRACT AND THE CAUSE OF ITS INCEPTION

In many cases of disease of the liver and biliary tract the bulk of the evidence seems to show that some form of hepatic damage has preceded

the onset of the illness and that it eludes diagnosis. In some cases the hepatic disability is demonstrated on the operating table as a gross change in connective tissue (cirrhosis) or as an interference with the portal circulation because of the presence of some degree of ascites. The presence of associated enlargement of the spleen indicates that some form of toxemia is present. The degree of hepatic damage thus shown varies a good deal, while in general the anatomic changes are more or less proportional to the amount of hepatic damage. The amount of reserve which is left, from which one may attempt to determine the prognosis, is not usually apparent, demonstrable or measureable.

A much greater degree of invisible pathologic change exists when jaundice appears. The change is always physicochemical and indicates severe changes and a state of emergency. When superimposed on any of the demonstrable changes mentioned in the preceding paragraph, it indicates a long-standing, perhaps usually an irreversible, pathologic condition. In many cases it indicates a terminal stage of the illness, and in any case a lack of hepatic reserve approaching the absolute. Commonly such a condition is associated with renal manifestations.

When the signs of the hepatorenal syndrome appear in such cases, one must assume that they represent a continuation of the preceding functional and anatomic pathologic process. In the absence of operative intervention the development of the picture is rather slow, although usually, as complete dissolution approaches, an apparent hastening of the process and a more rapid development seem to take place. When the alarming symptoms appear after an operation, it is probable that a measure of bacterial infection has been introduced, which, superimposed on whatever else has preceded, becomes "the straw which breaks the camel's back."

With acute or chronic cholecystitis and cholelithiasis, there is no doubt that some, at least, of the patients who reach the operating table have no such hepatic disturbance. Again, the bulk of the evidence seems to show that the hepatic or hepatorenal symptoms and lesions are then due primarily to bacterial infection and secondarily to later appearing, complicating conditions; the latter have all been previously indicated.

In cases of trauma producing pulpification of hepatic tissue a combination of causes seems to be operative. This may include the development of a tissue toxin, the secondary introduction of bacterial infection and the changes which accompany the appearance of any form of jaundice.

Whatever disturbance occurs is intensely magnified if jaundice is present. The abnormality depends on either or both of two factors: (1) the presence of obstruction of the major duct and (2) the state of the liver cell filter, which either is competent, in which case no

jaundice occurs, or is incompetent or interfered with, when jaundice follows. It seems to me that in cases in which trauma is present the appearance of hemolytic jaundice is of little practical importance because of the amount of blood extravasated and reabsorbed and because of other demonstrable factors.

VALUE OF TESTS OF HEPATIC FUNCTION AND/OR DAMAGE

The many chemical and biologic tests which have been proposed for the study of hepatic damage are bound up with tests of hepatic function. Dye excretion tests of many sorts and chemical tests based on metabolic change have been tried out and found disappointing. In most cases hepatic function is demonstrably maintained by compensatory effort, as bile is still present in the stool, since there is no impairment in glycogenesis or any evidence of failure to deamidize the amino acids, in that urea formation is unhampered and a progressive increase of nitrogenous products in the blood is observed. The clinical picture of well established disease, marked by abdominal distention, vomiting, rise in temperature, oliguria, appearance of albumin, casts and red cells in the urine, increase of residual nitrogen in the blood bleeding into the mucous surfaces and blood in the vomitus and the stool, indicates only too well the severity of the illness and the fact that coma and death are approaching. For that reason it is imperative to know the manifestations, which I pointed out some years ago, that indicate that such a severe and perhaps fatal condition is approaching. These are as follows:

1. Severe general symptoms, especially fever and chills. This item is possibly of least importance.

2. Anorexia or vomiting beyond the temporary or mild forms observable in the early stages of extrahepatic lesions of the biliary tract.

3. Shrinkage of the liver. This does not include the shrinkage of a temporarily swollen liver back to normal size. When this evidence is reliable and indicates a decrease below normal, it becomes the most important single clinical indication of destruction of hepatic cells and impending hepatic toxemia. The ultimate stage of such shrinkage is that known ordinarily as acute yellow atrophy.

4. Increasing jaundice.

5. Any tendency to hemorrhage.

6. Diminution of the secretion of urine, not accounted for by a corresponding diminution in the intake of fluid and with or without laboratory evidence of diminished renal function.

7. Demonstration of leucine or tyrosine in the urine.

8. Retention of nitrogen in the blood.

9. Signs of disturbed cerebral function—convulsions, stupor and coma. These are evidences of impending or established hepatic ("cholemia") or of hepatorenal ("uremia") intoxication.

In cases in which operation has been performed additional facts are available:

10. An operatively demonstrated cirrhotic condition of the liver. This indicates far advanced disease and one in which terminal manifestations may occur at any time. The presence of any degree of ascites only intensifies the significance of such findings.

11. Undue prolongation of postoperative vomiting for which no other competent cause is demonstrable.

12. Sudden and large diminution in the discharge of bile from an external biliary fistula, other facts and factors remaining equal and unchanged.

13. Marked diminution in the amount of bile in the stool in the absence of a discharging biliary sinus, other factors remaining equal.

14. Appearance of postoperative jaundice or any pronounced increase in previously existing jaundice.

It follows from all of these facts that the best and most competent idea of hepatic damage must still be based on more or less purely clinical grounds and that laboratory aid, while it may in some cases corroborate clinical impressions, is of little practical use. If a measure of the risk of any contemplated operation is to be attempted, or if, operation having been done, an opinion as to the prognosis is to be made, it must also be based on clinical observation, insight and experience, aided, to some extent, by laboratory data.

RENAL ELEMENT AND THE VALUE OF FUNCTIONAL TESTS

In 1911 Clairmont and von Haberer reported 5 cases of renal failure following operation on the biliary tract, in 3 of which fatality occurred. In the same year Steinthal noted anuria on the fourth day after operation on the common bile duct; autopsy showed acute tubular degeneration of the kidney. In 1911 von Beck and Simon witnessed death from uremia of patients on whom no operation had been performed. In 1921 Stäheli reported a case in which cholecystectomy and choledochostomy had been followed by death and referred to a similar case of Kehr. In 1922 Walters and Parham reported several instances of death from renal insufficiency after operation on the biliary tract. An extended report on the same subject was made by Wilensky and Colp in 1927. In 1933 Bartlett discussed and emphasized the renal factor in delayed death in the hepatorenal syndrome. Important experimental work was also done by Rowntree, Snell and Greene and by many others.

EFFECT OF THE EXCRETION OF BILE THROUGH THE KIDNEYS

The passage of bile and biliary components through the kidney, which occurs in cases of biliary obstruction, is usually, although not always, productive of renal abnormalities recognized clinically by the presence of albumin and casts in the urine. In cases of mild or early involvement an increase in the nitrogen content of the blood is not always demonstrable. This probably is the reason why the experimental work of Clairmont and von Haberer and that of Rowntree, Snell and Greene did not produce any retention of nitrogenous bodies in the blood, even though in their clinical observations Clairmont and von Haberer found evidence of renal failure in the jaundiced patient. Stäheli emphasized the importance of the duration of the hepatic disturbance.

The experience of the Mayo Clinic, as given by Walters and Parham, confirms the fact that in cases of severe involvement the influence of any hepatic disturbance on the renal mechanism is marked.

Hepatic insufficiency . . . differs from renal insufficiency; associated with the former there is abundant drainage of light colored bile, containing small amounts of the bile pigments. Patients become restless, then drowsy and stuporous, and finally succumb. During the entire course of the hepatic insufficiency little change occurs in content or volume of the urine, and the blood urea remains persistently low. Renal insufficiency is associated with the cessation of the drainage of bile. But with the cessation of drainage, evidence is shown in the urine from day to day of a progressive nephritis. During this period of renal insufficiency secondary to the damming back of the bile in the circulation, the jaundice deepens, the coagulation time of the blood lengthens, and the blood urea progressively ascends to the level of uremia.

RELATION OF THE RENAL TO THE HEPATIC LESION

From the facts outlined in this communication, it seems that renal effects occur because of two preceding circumstances:

1. Certain functional and anatomic changes occur in the hepatic cell and its environment which produce profound changes in normal hepatic metabolism, in that normal products are prevented from being excreted and normally and customarily produced, or abnormally produced and unaccustomed toxic bodies are prevented from being detoxified or neutralized. The resultant clinical picture I have previously designated as "hepatic toxemia," a primary effect of the initial disease.

In many cases (though not in all) the kidney, which after the liver is the great excretory and detoxifying organ of the body, fails to take up the latter function of the liver when the liver breaks down, because the kidney is not normally fitted to handle many of the normal products of hepatic metabolism or the abnormal toxic bodies liberated in the damaged liver cell environment. The kidney promptly breaks down in

its turn and becomes an important and frequently a decisive factor in the total subsequent dissolution. This is the secondary effect (the third or last stage), which clinically I have previously designated as "renal toxemia."

2. When the preceding source of the entire disturbance is not in the liver proper, as indicated previously in this communication (for example, destruction of tissue in burns), or when the original cause is bacterial infection, and especially when the distribution of the causative changes occurs either partly or wholly by paths not traversing the portal area, renal symptoms can occur independent of any preceding hepatic symptoms. Under such circumstances any hepatic symptom which may be present is probably concomitant.

DISTURBANCE OF RENAL FUNCTION

In clinical practice functional disturbance in the kidneys is best measured by the degree and extent of any accompanying azotemia. Azotemia occurs in association with the following conditions:

1. Severe and protracted vomiting.

2. Immoderate and severe loss of intestinal contents either through the natural exit or through an artificially produced intestinal fistula, especially when it is present high up in the alimentary canal.

3. Diabetes with acidosis, especially in the stage of coma.

4. Hypofunction (Addison's disease) or experimental removal of the adrenal glands.

5. Traumatic shock.

6. Extensive burns.

7. Acute coronary thrombosis.

8. Profuse hemorrhage.

9. Diseases of the liver and biliary tract such as are under discussion in this communication.

10. Circulatory failure and collapse following operation, trauma or disease.

A considerable degree of azotemia may exist without any apparent effect on the symptoms or on the clinical picture. Usually, however, there are asthenia, vomiting, failure of appetite and disturbances of the sensorium. It is difficult to estimate the role of vomiting. Often it ushers in the disturbance; in other instances it occurs after azotemia is discovered; in many cases the one seems to accentuate the other, and a vicious circle is established.

The urine may be normal; commonly, however, the usual laboratory evidences of "nephritis" are present. Various degrees of oliguria are present; complete anuria, however, never occurs. Sometimes, especially

in the presence of extrahepatic symptoms, the opposite state exists, and normal or even abnormally large amounts of urine are secreted and voided. The concentration of the urine is variable. The disturbance is often reversible to normal after satisfactory intravenous administration of abundant fluids containing salt and sugar and sometimes of whole blood. Sooner or later pronounced peripheral circulatory failure occurs when death is to be expected, and an index of improvement in any such vascular condition is an increase in the peripheral blood pressure.

RENAL LESIONS IN THE PRESENCE OF DEMONSTRABLE AZOTEMIA

It seems to be a fact that a renal lesion is not always demonstrable morphologically in the presence of azotemia. (I do not refer here to those changes in structure which are commonly seen in patients who are afflicted with long-drawn-out and devitalizing illnesses.) Extensive lesions are commonly present, however. The mechanism of production of such lesions and/or functional disturbances seems to be intimately associated with increased protein destruction, with alkalosis, with hypochloremia, with low pressure in the small peripheral arteries, with dehydration, with decreased flow of blood and with diminished volume of blood. The most important of these seem to be dehydration and diminished blood volume, and in certain quarters the entire concept of the disease is being built on these two factors. The cause of all of this disturbance is apparently obscure; it is undoubtedly a toxin, the origin of which is most likely to be found in disorder of the intestinal tract, in bacterial infection, in autolysis of tissue or in combinations of these with each other or with even more obscure factors.

CLINICAL VALUE OF TESTS OF RENAL FUNCTION AND OF ESTIMATIONS OF THE EXTENT OF AZOTEMIA

For scientific purposes estimations of renal function in cases of biliary obstruction are most valuable, as they indicate disturbances which otherwise are not demonstrable. Abramson, in 15 cases of jaundice due to various causes, was not able to discover clinical evidence of impairment of renal function by estimations of the nitrogen, water or salt content of the blood or by determination of the ability of the kidneys to excrete phenolsulfonphthalein. Haessler, Rous and Broun, Hanner and Whipple, Moller and Lunsgaard, Chabanier and Gaume, Wakefield, Power and Keith, Nolhard and Fahr and others have worked on this problem and have been rewarded with varying results, none of which is decisive enough to be of clinical or scientific value. The truth of the matter seems to rest on the extraordinarily large reserve and recuperative power of the liver and kidney, and, as has been pointed out so many times, a decisive answer is not available until practically all of the

reserve is gone and no power of recuperation remains. In addition, as I have pointed out, no single isolated determination is of value; what is of value is a succession of determinations in the same case, done with similar technic and by the same technician. In such a series the results tell much more accurately whether the process is progressive or regressive.

The renal complication, or rather, the stage in which combined hepatorenal symptoms appear, occurs most often in cases of jaundice; yet it occurs in cases in which jaundice is absent. Sometimes it is possible to detect the renal disturbance in its infancy. It is impossible to say to what stage the hepatic disturbance must progress before clinical evidence of renal involvement can be obtained by functional tests, which, up to the present writing, are notoriously unsatisfactory. However, as I have pointed out, the renal mechanism furnishes a satisfactory means of detecting any preceding change in the liver; any significant change in the kidney could, therefore, in properly selected cases be employed, other things being equal, as a measure of any otherwise unrecognizable disturbance in the liver. This is the value of tests of renal function in the presence of the hepatorenal syndrome.

SUMMARY

In clinical medical and surgical practice there is widespread distribution of hepatorenal symptoms and/or lesions. Such conditions are caused by various forms of poisoning; they may be associated with abnormal physiologic states; they follow various forms of disease due to obscure causes or to frank bacterial infection; they occur in association with disturbances of the ductless glands, notably with thyrotoxicosis, with mechanical obstructions of excretory passages or the sudden release of the same and, finally, with traumatic conditions, including mechanical destructive effects and the disintegrating effects of chemicals or heat.

One cannot escape the conclusion that the association of hepatic and renal pathologic conditions of the human body is almost necessarily frequent, because of the primary essential fact that the two organs are the chief means of excretion after metabolic change has taken place; because one of them, the liver, is the chief agent for neutralization of poisonous chemical bodies absorbed from the alimentary tract, either introduced as such through its portal of entry or elaborated within its length during the process of digestion; because the portal area is important in the destruction of bacteria and the detoxification of bacterial toxins; because the second of these organs, the kidney, is the chief means of elimination of poisonous bodies which the body finds it impossible to neutralize; because the kidney takes on the eliminatory

function of the liver when the excretory passages of the liver become incapable of functioning (by mechanical blockage, inflammatory swelling, or destruction of the secreting layer of cells), and because the kidney excretes living bacteria from the blood stream.

It seems that in all of the conditions hereinbefore detailed the two essential factors in the syndrome under discussion—hepatic and/or renal symptoms and/or lesions—do not occur in every case and do not always occur in the same intensity and proportion. They occur, however, sufficiently commonly in every variety discussed to make it fairly certain that the hepatorenal symptoms and/or lesions occur as a consequence of more than one essential cause.

One is compelled to conclude that whatever the beginning and development of the hepatic lesions and their concomitant, subsequent or (rarely) preceding renal lesion may be, the ultimate generic cause is a poisonous body of some kind, which passes through the liver and kidney. Such a poison may arrive from an exogenous source or develop within the body. It may be an effect of chemical drugs and poisons, a toxin resulting from bacterial growth or a product of destruction of the various tissues of the body. It may be formed during metabolism or may be split off as a side product of digestion. Whatever the poisonous body may be, it has the same action on one or both of these two extremely important excretory organs. Sometimes a similar action takes place on other parenchymatous organs. Frequently secondary toxic bodies are formed, more often in the liver than in the kidney, having been manufactured during the disturbance, or (being already domiciled there but unneutralized) having been activated by the disturbance, which adversely affects the liver and engages the kidney in similar degenerative and necrotic changes. There are demonstrable pylogenetic reasons for this peculiar complementary nature of the clinical phenomena and the anatomic manifestations.

Once this train of functional and anatomic disturbances begins, other factors come into play, such as fever, shock, autolysis of tissue, anoxemia, anhydremia and azotemia. All of these aid and abet the primary agents or even each other, by producing conditions which are capable of creating, or are found associated with, similar cellular degenerations in these parenchymatous organs. As must be apparent, the amount of overlapping in the various manifestations of all the conditions discussed is enormous. A vicious circle, therefore, is produced, and the primary injury is enormously accentuated.

The differences in duration of the development of this clinical complex, in the symptoms, in the suddenness and dramatic effect of the clinical manifestations and in the rapid culmination in death, the more protracted course or the occasional—or, perhaps, more frequent than

is believed—recovery, seem to have important relations to the size of the dose of the causative agent, to the time limit in which the latter is delivered and to various forms of preceding sensitization of the body to diverse toxic bodies. This seems to be the correct view of the whole question of hepatorenal involvement.

There seems to be no biologic or clinical connection between the hyperpyrexia or so-called liver death and the protracted form of disease of the liver and kidney, the so-called hepatorenal syndrome. Liver death is probably related to some form of hyperacute bacterial infection. The hepatorenal complex reviewed and discussed in this communication seems to be something entirely different.

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EFFECTS OF HEMORRHAGE AND OF TRANSFUSION ON THE BLOOD FLOW IN AN EXTREMITY

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The relation between the blood pressure and the peripheral flow of blood is of interest in view of certain recent opinions on the mechanism of surgical shock (Freeman,[1] Meek,[2] Roome[3]). It has been suggested, and supported to various extents, by these authors that shock arises by the following mechanism: A marked reduction of the peripheral flow occurs as the result of a diminished blood volume and/or sympathico-adrenal activity; this ischemia produces capillary injury, with increased permeability, permitting a generalized loss of blood plasma, which finally progresses to peripheral circulatory failure.

Poiseuille and others[4] have exhaustively studied the relation existing between the head of pressure (P) and the volume flow (F) of homogeneous fluids in small rigid tubes. Under these conditions F is proportional to P, the ratio P/F is a constant and the relation is graphically linear. These observations, however, cannot be directly applied to the flow of blood in the peripheral circulation, because of the distensibility of the vessel walls and the corpuscular nature of the blood. Further modification of the relation may be anticipated in the intact animal during hemorrhage or shock (and in certain other conditions), owing to vasomotor activity and to changes in the blood concentration.

Previous studies of the P/F relation in the peripheral circulation have given somewhat divergent results. Whittaker and Winton[5] described it as linear and reported that the flow of blood in an isolated limb became zero at pressures of 20 to 30 millimeters of mercury and below. Norris, Bazett, and McMillan[6] described F as proportional to

1. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: J. Clin. Investigation 15:651, 1936.

2. Meek, W. J.: Northwest Med. 35:325, 1936.

3. Roome, N. W.: Anesth. & Analg. 17:237, 1938.

4. Poiseuille and others, cited by Schoder, E. W., in Marks, L. S.: Mechanical Engineers' Handbook, ed. 2, New York, McGraw-Hill Book Company, 1924, p. 231.

5. Whittaker, S. R. F., and Winton, F. R.: J. Physiol. 78:339, 1933.

6. Norris, G. W.; Bazett, H. C., and McMillan, T. M.: Blood Pressure: Its Clinical Applications, Philadelphia, Lea & Febiger, 1927, p. 39.

$P^{3/2}$ rather than directly, and Barcroft and Samaan[7] represented graphically a similar nonlinear relation.

In the present experiments the effect of graded hemorrhage on the blood pressure and the peripheral blood flow was studied in the intact animal. In some cases the effect of replacement of the blood was observed.

METHODS

The femoral blood flow was measured for 7 dogs anesthetized with pentobarbital sodium, by means of a photoelectric strohmuhr.[8] The blood pressure was measured by a mercury manometer at the inlet to the limb (distal to the strohmuhr). The
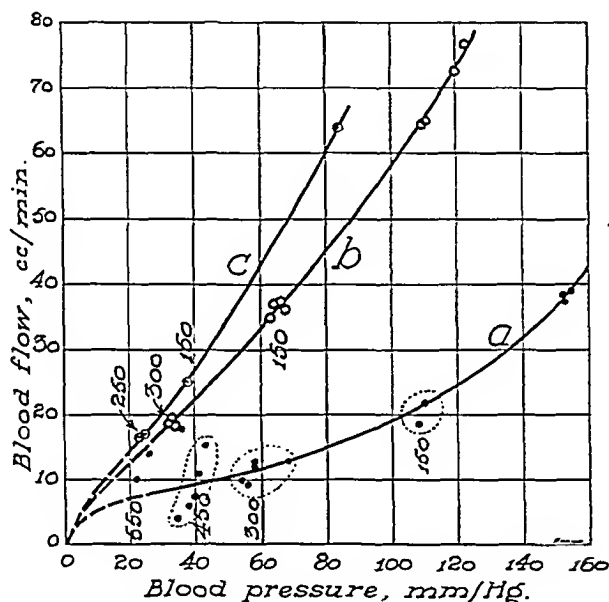
Chart 1.—P/F relations in the intact hindlimb of dog 13 (weight 10.5 Kg.). Curve *a* shows the first curve obtained, curve *b* the effect of exsanguination and transfusion and curve *c* a third graded hemorrhage after denervation. The numbers beside each curve indicate in cubic centimeters the amount of blood withdrawn.

blood pressure was lowered by graded hemorrhage, and in 3 cases the blood was replaced after the pressure had fallen to levels of 20 to 40 millimeters of mercury. In 3 experiments the limb was acutely denervated by section of the sciatic and femoral nerves. In 1 experiment the animal was exsanguinated as completely as possible and the blood replaced just before death; this was thought to represent an exhausted state, probably with marked atonicity of the vessels of the limb and with nearly maximal blood dilution. Two experiments were made with the use of saline solution from a reservoir to perfuse an isolated limb.

7. Barcroft, H.. and Samaan, A.: J. Physiol. **85**:47, 1935.
8. Roome, N. W.: Am. J. Physiol. **123**:543, 1938.
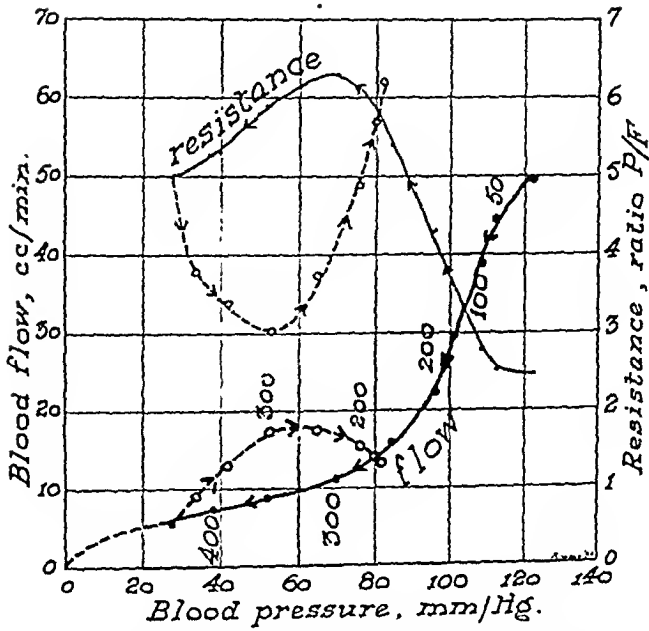
Chart 2.—P/F relations and numerical values for this ratio in dog 26 (weight 15.5 Kg.), acutely denervated. Note that on transfusion (broken line) the flow is greater and the ratio correspondingly less than during graded hemorrhage (solid line). The numbers beside the curves indicate the blood deficit, in cubic centimeters.
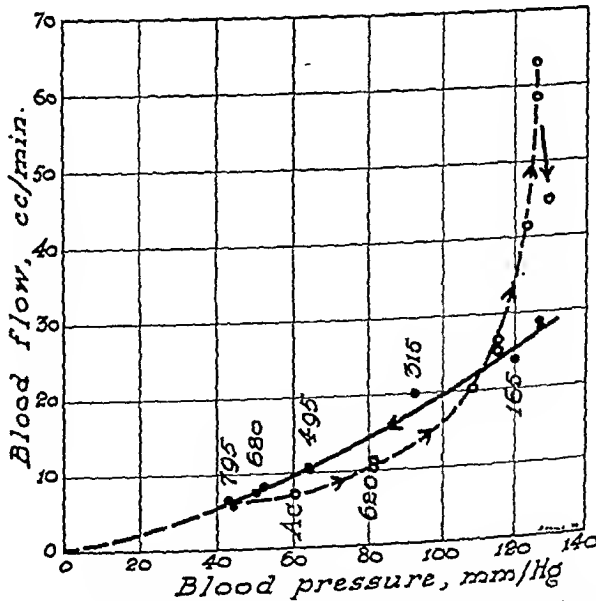
Chart 3.—P/F relations in dog 43 (weight 19.7 Kg.), showing the effect of hemorrhage (solid line) and of transfusion (broken line). Note that in this case the curve of transfusion fell below the curve of hemorrhage. The blood deficit is indicated in cubic centimeters; at *Ac*, 140 cc. of 10 per cent gum-saline solution (acacia) was given.
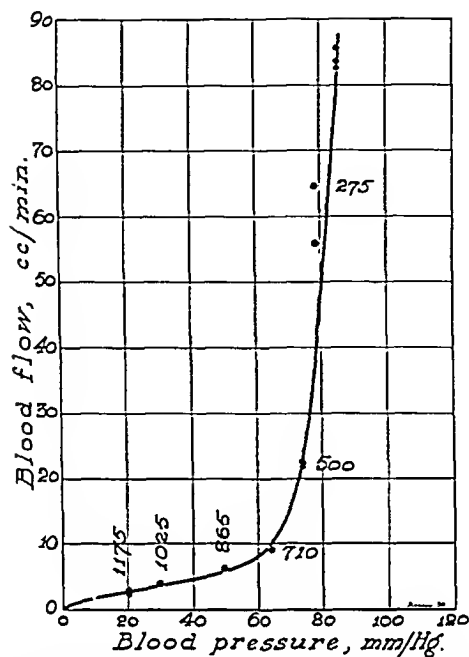
Chart 4.—P/F relations for dog 43, third curve, after denervation. Note the exceedingly low rates of flow with lowered pressures in this exhausted preparation.
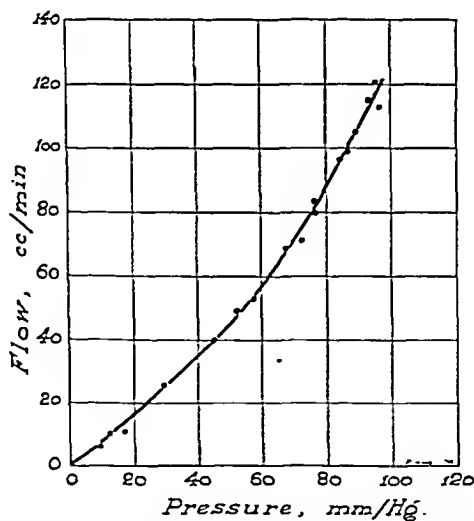
Chart 5.—P/F relations with saline perfusion of an isolated hindlimb (dog 15).

OBSERVATIONS

Typical curves showing the P/F relations in the intact limb are given in charts 1, 2, 3 and 4. In chart 1 it will be seen that the readings for a normal limb may be widely dispersed, particularly at the lower levels, and it is difficult to fit a curve to them. Smoother curves were obtained in the "exhausted" state and again after denervation.

The effect of replacement of the blood is variable. Chart 2 shows that the flow was abnormally great when the transfusion was begun and then fell off to about the expected level. Chart 3 indicates that the flow was less than expected and then rose above the previous curve. Chart 4 represents an experiment on the same animal which yielded the record shown in chart 3, with a second bleeding and transfusion intervening, and shows the excessively slow flow which occurs in some cases at low pressures.

The relation existing in the isolated limb when perfused with saline solution is shown in chart 5. It will be noted that this is a smooth curve, the characteristics of which fit fairly well the formula $F = m.P^n$, the values for n varying in different portions of the curve from 1.21 to 1.46.

COMMENT

The relation between the inlet pressure and the volume flow of blood in a limb of an intact animal during graded hemorrhage is thus an irregular curve and the ratio P/F a variable, tending (chart 2) first to increase as the pressure falls and then to diminish with further reduction of the pressure.

The explanation of the irregular relation no doubt depends on the interaction of the several factors mentioned previously as capable of distorting the linear relation of Poiseuille. First, because of the distensibility of the vessel walls, their diameter will increase with increased pressure, and the flow will be greater than the expectation from Poiseuille's law. Thus the ratio P/F will diminish as P increases, and the relation will be graphically expressed as a curve. Second, because the blood is a suspension of corpuscles relatively large in proportion to the smallest of the vessels they traverse, it would be possible that at low levels of pressure the volume flow would be abnormally reduced, producing further deviation from a linear relation. Third, in the intact animal during hemorrhage, since vasoconstriction occurs in response to the lowered blood pressure, further reduction of the volume flow at given values for pressure would result. These factors would all tend to reduce the flow at a given pressure below the expected level.

Two other factors tend to increase the flow at given pressures, thus opposing the three previously mentioned. These are, first. dilution of the blood by influx of fluid from the tissues in response to the bleeding.

which lowers the viscosity of the blood and increases the flow, and second, local dilatation or reactive hyperemia in response to the partial ischemia of reduced flows. It would seem that these factors would become important chiefly after there had been a considerable reduction of the blood pressure and of the blood flow. They would thus result in a diminution of the ratio P/F at the lower levels of P and F. That this occurs is well illustrated in chart 2, in which the ratio increases as the pressure falls, reaching a maximum at about 70 millimeters of mercury and then falling off as the pressure falls further.

For these reasons, then, the peripheral flow is markedly reduced with moderate blood losses and with slight depressions in the blood pressure. The flow then continues to fall slowly with further hemorrhage, while the blood pressure falls relatively rapidly. This correlates well with the finding of Blalock [9] that the cardiac output falls more rapidly than the blood pressure in response to hemorrhage. Exceedingly low levels of flow occasionally occurred with the lowered pressures (as shown in chart 4), but in no case did the flow entirely cease at the pressures studied. These reduced flows, which were only a few per cent of the normal, would constitute an essentially complete ischemia in the tissues. which supports the theory of the causation of shock previously outlined.

The effect of transfusion was variable, apparently depending on the degree of ischemia and the period for which it had been present, being distorted from the curve of hemorrhage by dilution and dilatation when the ischemia was marked and by constriction when it was less marked. It is of interest that in the experiment graphically shown in chart 2 both P and F were lower at the same levels of blood deficit during the transfusion than during the bleeding.

The relation of pressure to flow with perfusion of an isolated limb with saline solution was shown to approximate the formula $F = m.P^n$ when n is from 1.21 to 1.46.

SUMMARY AND CONCLUSIONS

The relation between pressure and flow in the peripheral circulation of dogs was studied and found to be an irregular curve. A marked diminution of flow occurs with moderate hemorrhage. This finding, with the observation of excessively retarded flow in some cases, lends support to the ischemic theory of shock.

9. Blalock, A.: Mechanism and Treatment of Experimental Shock: Shock Following Hemorrhage, Arch. Surg. **15**:762 (Nov.) 1927.

TOTAL PNEUMONECTOMY

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It is our purpose in this paper to report 2 cases in which total pneumonectomy was performed and to call attention to factors which may make for better results in the performance of an often difficult operation.

REPORT OF CASES

Case 1.—D. C., a white man aged 42, a manual laborer and plumber, was admitted to the service of Dr. S. A. Lowenberg on May 4, 1936. The chief complaint was sharp pains in the lower part of the chest on the left side. The patient had been well until two and one-half months before his admission to the hospital, when the pains referred to were noted. These were accompanied by cough, especially in the morning, productive of small amounts of foul-smelling and foul-tasting blood-tinged sputum. In the past eight weeks he had lost 24 pounds (10.8 Kg.). Night sweats had been present for three weeks. Dyspnea and palpitation were noted on exertion. The patient had been treated for addiction to morphine fifteen years ago. The family history revealed that a brother of the patient had died of cancer of the lip.

Physical examination showed a well nourished man who was not acutely ill. The chest was thin, with prominent supraclavicular fossae. An inspiratory lag and limitation of movement on the left were noted. Tactile fremitus and vocal fremitus were absent in the lower left quadrant of the chest posteriorly. Breath sounds were absent in the same area. A pleural friction rub was present at the base of the left lung anteriorly. At the apex of the heart was a soft mitral systolic murmur, not transmitted. The blood pressure was 112 mm. of mercury systolic and 70 diastolic.

A roentgenogram of the chest, taken on the day of admission, showed compensatory emphysema of the right lung, with flattening and compression of the right side of the diaphragm. The heart was not enlarged but was pulled over to the left. The left side of the diaphragm was obscured, and the position of the gas bubble in the stomach indicated that the position of this organ was higher than normal. There was atelectasis of the lower lobe of the left lung, with narrowing of the intercostal spaces in the left lower quadrant of the chest. There was no evidence of tuberculosis. The diagnosis was atelectasis of the lower lobe of the left lung, due to bronchial obstruction, inflammatory or malignant.

Bronchoscopic examination on May 6, by Dr. W. F. Moore, showed the left main stem bronchus below the opening of the bronchus of the upper lobe almost completely blocked by a new growth of tissue, which seemed to have its origin on the inner side. In this region the mucous membrane bled easily on touch. A

section was taken for laboratory examination. This had the clinical appearance of a bronchogenic malignant tumor, involving the left main stem bronchus below the level of the upper bronchus.

Microscopically the hyperplastic mucosal epithelium of the bronchus merged with the tumor, which formed irregular sheets of poorly differentiated prickle cells averaging less than one mitotic figure per high power field. There was
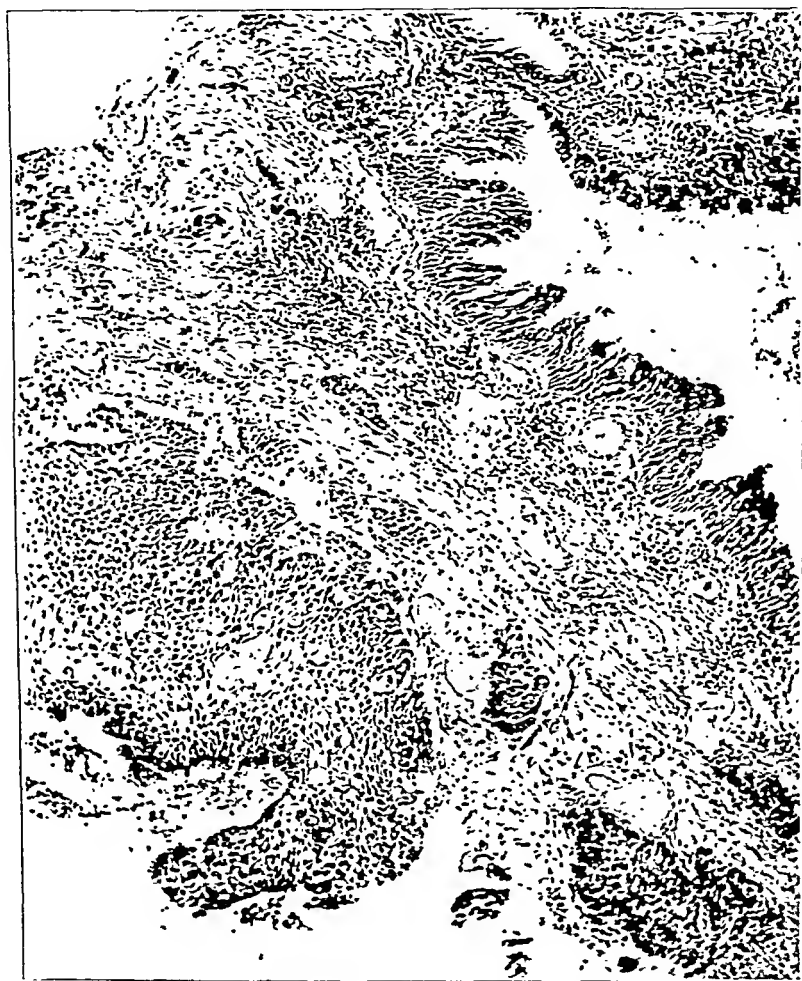
Fig. 1 (case 1).—Photomicrograph ($\times$ 115) showing the epithelial lining of the bronchus and also a squamous cell carcinoma. The carcinoma has formed islets and has invaded lymphatic spaces.

permeation of some mucosal lymphatics (fig. 1). The diagnosis was squamous cell carcinoma, type 3, of the bronchus.

On May 16 the patient was discharged to the radium clinic, where he received a course of six high voltage roentgen treatments, with appreciable benefit.

On June 1 the patient was readmitted to the hospital, to the surgical service of Dr. Moses Behrend. The temperature on admission was 102 F., but the patient did not appear acutely ill. The physical findings were essentially as before. On June 1 an initial pneumothorax was performed on the left side. A refill of 300 cc. was given. On June 3 a refill of 400 cc. was given. On June 5 a transfusion of 500 cc. of blood was given. On June 8, 200 cc. of air plus 50 cc. of 1 per cent peptone beef broth bouillon was injected into the pleural cavity. On June 10 an air refill of 250 cc. and a blood transfusion of 350 cc. were given.

On June 11 operation was performed with the patient under combined avertin with amylene hydrate and cyclopropane anesthesia. With the patient lying on the right side, incision was made over the third interspace on the left, from the sternum to the midaxillary line. The fibers of the pectoralis major muscle were cut across. The internal and external intercostal muscles were cut, and the pleura was opened in the third interspace. The upper lobe of the left lung was found to be almost completely collapsed as a result of the pneumothorax. The lower lobe was densely adherent, especially posteriorly and on its diaphragmatic surface. The hilar lymph glands were enlarged. Separation of these adhesions was extremely difficult and tedious. The mediastinal pleura was incised, and the left pulmonary artery and vein were ligated with silk. Despite this, considerable hemorrhage was encountered when an attempt was made to dissect out the left bronchus. The pedicle tourniquet of Carr was applied, and the lung was removed. At this point the patient's blood pressure fell sharply. Intravenous dextrose plus 350 cc. of blood was administered. Considerable free motion of the mediastinum was noted. The wound was closed with three heavy braided silk pericostal sutures. A small rubber drain tube was inserted in the eighth interspace. The patient left the operating room in grave condition and died shortly after returning to bed.

Summary.—In this case we were confronted with an inoperable condition. In view of the adhesions and the presence of carcinoma in the hilar glands, the operation should have been limited to exploration and biopsy.

CASE 2.—H. S., a white man aged 40, was admitted to the service of Dr. H. B. Shmookler on June 30, 1929, because of pain in the right side, excessive cough and expectoration with hemoptysis.

The family history disclosed nothing of importance. The patient had had rheumatic fever in 1917, with recurrent attacks in 1921 and 1923. A chronic cough with much expectoration had been present for the past fifteen years. The history of the present illness showed that on June 28 the patient was awakened by cough accompanied by hemoptysis of approximately 200 cc. On June 29 there was a recurrence of hemoptysis, amounting to 120 cc.

Physical examination on June 30 revealed a well nourished man. Examination of the chest showed the breath sounds suppressed and distant on the right side and normal on the left. Urinalysis and chemical studies of the blood gave negative results. The Wassermann reaction for syphilis was negative. The sputum showed no tubercle bacilli. The clinical diagnosis was bronchiectasis with ulceration.

Roentgen examination revealed an extensive pathologic process at the base of the right lung and below the ninth rib, with densely thickened pleura and pleural effusion. The lungs showed moderate peribronchial fibrosis throughout. The left side of the diaphragm was depressed; the right side of the diaphragm was completely obscured. The heart was slightly retracted to the right. Injection of iodized poppyseed oil 40 per cent into the middle lobe showed no abnormalities. The bronchi of the lower lobe were not filled.

The patient was readmitted on June 27, 1937, to the service of Dr. A. Trasoff because of hemoptysis of approximately 200 cc. While in the hospital he had two other periods of hemoptysis, in which equal amounts of blood were produced. Bronchoscopic examination by Dr. Lell at the time of this admission revealed the trachea completely filled with foul-smelling pus. On aspiration this was found to be emanating from all the bronchi on the right side. The left side was clear. A great deal of granulation tissue was present in the bronchi on the left, which bled easily on the slightest touch. Prior to this admission the patient had been receiving regular periodic bronchoscopic aspirations at another hospital. After this admission he was given such treatment at frequent intervals.

Fig. 2 (case 2).—Photomicrograph (× 5) showing a large, dilated bronchus with infiltration of the mucosa and wall by acute and chronic inflammatory cells. Note the areas of superficial mucosal ulceration.

Roentgen examination at this time showed increased density on the right side, extending from the apex to the base of the lung. There was marked fibrosis, probably with bronchiectasis, in the base of the left lung. The heart and trachea were retracted to the right.

The diagnosis was: atelectasis of the right lung, cavities in the upper lobe of the right lung, probably due to suppuration; fibrosis with probable bronchiectasis in the lower lobe of the left lung; retraction of the heart and the mediastinal contents.

The patient was seen at weekly intervals in the bronchoscopic clinic, where aspiration was carried out. He was readmitted to the hospital on November 8,

at which time hemoptysis had recurred; hemoptysis was present on admission. Cough and expectoration had increased since the last admission. On successive days the patient had hemoptysis of 120, 60, 200 and 540 cc. This condition was treated by blood transfusions at regular intervals. The sputum at this time was profuse and foul-smelling. Sixteen ounces of sputum in twenty-four hours was the average output. The patient was miserable and begged that something be done to relieve him.

Surgical consultation was held with Dr. Moses Behrend. The gravity of the situation from a surgical standpoint, in view of the long-standing suppurative disease, was noted. However, it was felt that total pneumonectomy offered the only
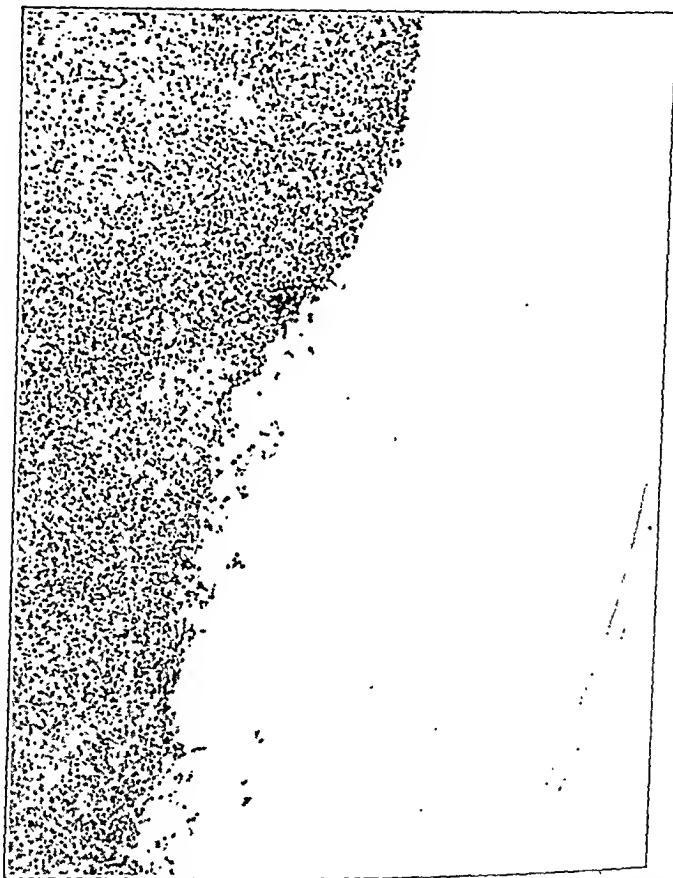
Fig. 3 (case 2).—Photomicrograph (× 100) showing the wall of one of the abscess cavities. The section itself shows dense infiltration by polymorphonuclear cells. Immediately beneath but not shown in the section is infected granulation tissue.

chance for return of health. This operation was advised. Artificial pneumothorax was not even attempted, as it was felt that there was no free pleural space. This was confirmed at operation.

On December 10, with the patient under intratracheal cyclopropane anesthesia, an incision was made (by Dr. J. Sigafoos), curving under the right breast. A skin flap was turned back so as to expose the pectoralis major muscle, which was incised in the third interspace, the incision being carried backward to the posterior axillary line. The third, fourth and fifth ribs were sectioned through their costal

cartilages. The pleural cavity was opened in the third interspace. The lung was found to be densely adherent in practically every portion to the parietal pleura. By gentle dissection it was freed at the apex and gradually was partially freed from the diaphragm, where it was so densely adherent that at one point the diaphragm was torn in separating it. This tear was repaired immediately with a catgut suture. The vessels of the hilus were then attacked, and effort was made to ligate them individually. However, adhesions at the hilus were so dense that this became practically impossible. Profuse bleeding occurred during dissection, and it was necessary to apply large curved clamps to the hilus to control hemorrhage. It was impossible to make use of the hilar tourniquet, because of the

Fig. 4 (case 2).—Photomicrograph (× 100) of an area of atelectatic lung, showing the bronchi and alveoli lined with altered epithelium. Note the replacement of many intervening alveoli by fibrous tissue and infiltrating chronic inflammatory cells.

adhesions. At the time the hilar structures were clamped a sharp drop in blood pressure occurred, and spontaneous respiratory movements ceased. The operation was temporarily halted, and full control of the patient was given to the anesthetist. After approximately ten minutes of artificial respiration spontaneous respiratory movements were instituted, and the blood pressure rose to a normal level. The operation was then completed by ligation of the vessels and the major bronchi with heavy catgut sutures. The hilar structures were then oversewn with a small amount of lung tissue which remained. At the time of operation it

appeared that the bronchus had been occluded close to the carina. This proved subsequently to be untrue. A stab wound was made in the eighth interspace in the axilla, and a soft rubber tube was inserted. The wound was closed in layers after the third and fourth ribs had been approximated with heavy braided silk pericostal sutures. The patient left the operating room in good condition. He was returned to his bed and immediately placed in an oxygen tent. A blood transfusion was given.

On December 12 the patient was not dyspneic. A transfusion of 500 cc. of blood was given. On December 12 respiration was more labored. Aspiration of the chest through the tube was done, and 150 cc. of brownish red fluid was obtained. Two hundred and fifty cubic centimeters of blood was given by transfusion. On December 13 respirations were moist and labored. A laryngoscope was passed by Dr. J. G. Sirken, and the trachea was aspirated, with immediate relief. This aspiration was repeated with good effect on the following day. Thereafter it was not necessary. The patient did well until December 28, at which time a bronchial fistula developed, with immediate increase in the amount of sputum. On Jan. 3, 1938, in an effort to locate the site of the fistula, a small incision was made with the region under local anesthesia. At this time some necrotic particles of lung tissue were removed. The fistula was in such a position that it could not be reached at this time. A rubber tube was reinserted for drainage.

On January 11 there was a sudden attack of coughing accompanied by expectoration of 3 ounces (30 cc.) of blood. The following day there was a sudden large hemoptysis, during which the patient died. Postmortem examination revealed a small bronchial fistula arising from one of the bronchi of the upper lobe. There was a piece of the bronchus of the lower lobe, approximately 4 cm. in length, remaining. To this was attached a piece of collapsed lung tissue representing a small portion of the lower lobe. When this bronchus was opened it was found to be filled with blood which apparently arose from the mucous membrane. The mucous membrane was of the hyperplastic type described at the time of bronchoscopic drainage.

Summary.—This case presents another patient on the borderline of operability. Inflammatory disease of the lung was of long standing, and normal landmarks were obliterated; this prevented accurate dissection of the bronchus. However, we feel that if that portion of the bronchus that was inadvertently left behind had been removed, the patient would have made a good recovery.

PREOPERATIVE CARE

The success or failure of any operation may depend on the presence or absence of some well laid plan of attack. An operation of such magnitude as complete pneumonectomy cannot be undertaken haphazardly, and proper preoperative management is an important factor in the achievement of a successful result. As time goes on and greater experience is gained in the experimental laboratory and the operating theater we will continue to improve our results. At present we feel that certain measures are of definite value.

Preoperative blood transfusion is of value in this as in other surgical procedures when the figures for hemoglobin and for the total count of red blood cells are lowered. Hemoptysis is commonly associated with suppurative disease of the lungs and bronchi and is often the

presenting symptom in cases of malignant tumor. Pulmonary suppuration of even short duration usually causes some degree of secondary anemia.

Artificial pneumothorax is an important preliminary adjunct to operation and should be instituted seven or eight days before operation is performed, if possible. It is an aid at times in the localization and diagnosis of intrathoracic neoplasm. In the presence of suppurative disease it may decrease the amount of purulent material in the lung, lessening the likelihood of spill to the contralateral side at the time of operation. Furthermore, the patient becomes accustomed to a lower vital capacity, and the intrathoracic pressure approaches that which will be present at the time of operation. When the mediastinum is mobile, artificial pneumothorax will cause a gradual displacement which may be compensated for rather than a sudden one which may embarrass the circulation. Increased expansion of the contralateral lung occurs, the better to carry out the respiratory function, and here again the prospective postoperative physiologic condition is approached.

In addition to preoperative artificial pneumothorax, Rienhoff [1] has advocated the introduction of a solution of peptone into the thoracic cavity preoperatively in order to stimulate the formation of an exudate which might later organize and aid in the obliteration of the space remaining after removal of the diseased lung. The injection was carried out in our first case but not in subsequent cases. Our present attitude is that such injections are not requisite, for reasons which will be discussed under postoperative management. We know from the results of our experimental work that the space left by removal of a lung tends gradually to become smaller because of the enlargement of the remaining lung, because of the shift of the mediastinum to the side on which operation was done and because of a gradual natural collapse of the thoracic cage on the affected side, particularly in young persons. When the diaphragm is paralyzed by section of the phrenic nerve it rises and further helps to obliterate the space. If symptoms should develop as a result of absorption of the air left in the thorax at the time of operation, refills may be instituted at regular intervals. Finally, thoracoplasty may be performed to abolish dead space and is, in fact, obligatory if extensive infection of the pleural cavity has occurred as a consequence of operation.

Cooperation of the bronchoscopist is desirable in the treatment of patients whose clinical course has been characterized by expectoration of appreciable amounts of purulent sputum. Such patients should have the benefit of bronchoscopic aspiration immediately prior to surgical

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1. Rienhoff, W. F., Jr.: The Surgical Technic of Total Pneumonectomy: Arch. Surg. **32**:218 (Feb.) 1936.

removal of the diseased lung tissue. Bronchoscopy is performed with the region under local anesthesia, and since nearly all patients have had previous therapeutic or diagnostic bronchoscopic examinations little additional mental or physical trauma is added to that of the major operation. The benefits of such preoperative treatments are obvious.

There has been a tendency, we feel, for bronchoscopists and clinicians together to continue for too long a period conservative treatment of patients who cannot permanently benefit from such treatment. Consequently the patients are often in poor physical condition at the time of operation and present an unnecessarily increased risk to the surgeon. At the time operation is performed it is found that irreversible intrathoracic changes have already occurred.

ANESTHESIA

In operations on the lungs the maintenance of a competent airway is a matter of paramount importance. For this purpose the use of the intratracheal tube is of great aid. When the maintenance of respiratory function depends on the integrity of a single main stem bronchus the normal margin of safety is immediately halved. Any spill of purulent or sanguineous secretion must be promptly aspirated during the course of the operation; otherwise symptoms of oxygen lack will soon appear. and its effects on the cardiac muscle rapidly become evident. Breathing becomes forced. The respiratory movements are exaggerated, and the operative procedure must be delayed until they are once more quiet. If this condition is not promptly relieved, cardiac action increases in rapidity and in a short time may become irregular. The blood pressure falls, and suffocation is complicated by cardiac failure. These alarming manifestations may be prevented or promptly relieved by aspiration of the offending secretions through a thin catheter inserted through the intratracheal tube or beside it. In the case in which operation was performed for chronic suppurative disease of long standing the patient had expectorated from 30 to 250 cc. of sputum daily for at least fifteen years. Despite the fact that he had been subjected to bronchoscopic aspirations immediately prior to operation and several ounces of purulent secretion had been removed by this means, it was necessary to aspirate through the intratracheal tube at frequent intervals during the operation, and several ounces more of thick, tenacious mucopurulent sputum was recovered by this means. Had such a device not been utilizable. completion of the operation would have been impossible. In a lesser degree but in a no less important one such intratracheal control may become requisite in operations for malignant disease. Primary carcinoma of the bronchus almost invariably causes some bronchial obstruc-

tion, and with this occurs a damming back of secretions which frequently become purulent. Bronchiectasis and abscess of the lung occurring distal to the point of obstruction and secondary to bronchial carcinoma are usual rather than exceptional. One of the chief complaints of the patient operated on for malignant tumor was expectoration of foul-smelling sputum. During the manipulations attendant on removal of the offending lung these secretions can scarcely fail to be at least partially forced past the obstruction, after which they find their way to the trachea.

We believe the anesthetic of choice to be cyclopropane. Its skilful use enables the patient to maintain respiratory function by shallow, quiet breathing. which renders operation easier. The high percentage of oxygen available when cyclopropane is employed is an aid to more rapid readjustment of the oxygen saturation of the blood after the occlusion of one bronchus. In operations on the lung the appearance of cyanosis augurs ill, and in the presence of a competent airway it does not occur when cyclopropane is administered.

Burnett [2] has used local and regional anesthesia in the performance of pneumonectomy and has demonstrated its value. However, we feel that better control of the patient is obtained by means of intratracheal anesthesia.

The presence of an alert and competent anesthetist is most important at the time we choose to call the "critical period" of the operation. We refer to the moment at which the bronchus is clamped and the five minute period immediately following it. In experiments on dogs [3] we found that although the animal might be breathing quietly during manipulation of the lung and while the pulmonary vessels were being individually ligated, sudden occlusion of the main stem bronchus by a clamp usually resulted in a brief period of struggle, accompanied by respiratory and cardiac irregularity. From this the animals quickly recovered. A similar phenomenon occurs frequently but not invariably in man. One of us has seen 2 patients die within five minutes of the time of occlusion of the main stem bronchus, although their condition had been satisfactory before this time. In the case in which we operated for malignant disease no untoward reaction was observed. However. in the patient operated on for suppurative disease, when the bronchus was clamped the respiratory movements ceased, the cardiac action became irregular and the blood pressure promptly dropped to 70 mm.

2. Burnett. W. E.:   One Stage Pneumonectomy Under Local Anesthesia: Successful Case Reported. J. Thoracic Surg. 6:458 (April) 1936.

3. Behrend. A.. and Mann. F. C.:   Some Postoperative Effects of Pneumonectomy: A Morphologic Study. J. Thoracic Surg. 6:685 (Aug.) 1937. Thomas, L. C.; Behrend. A., and Mann. F. C.: Experimental Pneumonectomy, ibid. 6:677 (Aug.) 1937.

of mercury (systolic). The operation was immediately halted, and a hot compress was applied to cover the incision. The anesthetist was given complete charge of the patient. Respiration was maintained artificially with relaxation of the rebreathing bag attached to the anesthetic machine. Within five minutes the patient took his first voluntary inspiratory gasp. This was soon followed by a resumption of normal respiratory movements, and the blood pressure returned to its former level. The operation was carried on to completion without a further similar incident. We would stress particularly that it is important that the operation should be temporarily abandoned so that the anesthetist may have complete control of the patient. Too frequently a sudden cessation of respiration and rapid drop in blood pressure are followed by the trauma of additional operative procedures which are frequently hurried in an effort to complete the operation. This adds insult to the injury sustained, and frequently the patient is unable to withstand the added trauma.

OPERATIVE TECHNIC

We have found that the following position and incision give adequate exposure for removal of a lung. The patient lies on the back, the optimum position for anesthesia, on a small pillow placed so that the side to be operated on is raised off the table from 2 to 3 inches (5 to 7.5 cm.). The arms are both extended at shoulder height on armboards. Extension of the arm on the side of operation keeps it out of the way, raises the scapula on that side and enables the incision to be curved posteriorly. Extension of the arm on the opposite side makes it readily available for intravenous administration of fluids. This is usually begun early in the course of operation. Five per cent dextrose in physiologic solution of sodium chloride is given, and 6 per cent solution of acacia or citrated blood is given if the indications for it arise.

We prefer a parasternal flap incision curving under the breast and carried to the posterior axillary line. It allows closure of the wound in overlapping layers. The pectoralis major muscle is split over the third intercostal space. After the intercostal muscles have been divided the pleural cavity is entered and manually explored. If no contraindication to further exploration is encountered, the third, fourth and fifth ribs are sectioned at the costosternal border, and a self-retaining rib spreader is inserted. This gives a fuller view of the lung and mediastinum. The lung is then mobilized by being freed from any attachment it may have to the parietal pleura or to the mediastinum and by section of the pulmonary ligament. The pulmonary vessels are individually ligated, and the bronchus is clamped and cut separately. The importance of preserving a good blood supply to aid healing of the occluded bronchus has been demonstrated experimentally. If it is possible to

clamp the bronchus in such a manner that the bronchial vessels are not damaged, double ligation with braided silk will suffice. If the bronchial vessels are occluded by the clamps, the end of the bronchus should be closed with interrupted silk sutures. In any event it is most important to bury the bronchus by overlapping it with the adjacent pleura or any remaining lung tissue.

The greatest obstacle to careful operation and clean dissection is presented by diffuse adhesions to the pleural surfaces. Dense adhesions were present in both cases reported here, and the lung was separated with the greatest difficulty. Operability was doubtful in both cases but was nevertheless undertaken. In the first case it was necessary to pass a mass ligature with the hilar tourniquet, while in the second case the adhesions were so dense that it was impossible to apply the tourniquet and it was necessary to put several large curved hemostats on the hilus because of hemorrhage of alarming proportions occurring at the time of dissection of the hilar structures. It was impossible to dissect the right main bronchus as far as its bifurcation. Inability to do so led to the eventual death of the patient, for the autopsy specimen revealed the source of the final hemorrhage to be the mucous membrane of that small portion of the right main bronchus that remained as a result of the surgeon's inability to make a clean bronchial dissection. It is fully as important to know when not to proceed with total pneumonectomy as it is to understand the technic of the operation. In some cases inflammatory adhesions may be so great as to render continuation of the operation inadvisable. On the other hand, freeing of the adhesions in one stage and removal of the lung at the subsequent operation is a sensible procedure, particularly if the patient's condition at operation becomes in any way critical. In cases of malignant tumor, manual and microscopic examination (frozen section) of the mediastinal glands before removal of the lung is important. In our case of malignant tumor the carcinoma was observed to extend into the contralateral lung, but this did not become apparent until examination was made post mortem. Roentgenographic, clinical and operative examinations failed to reveal .the presence of malignant disease in the "good" lung.

POSTOPERATIVE CARE

After the pneumonectomy the patient should be placed in a bed raised at the foot, so that his head is dependent. This position facilitates tracheal drainage and is an important factor in the prevention of an aspiration type of pneumonia or atelectasis attributable to bronchial plugging, particularly when cough is suppressed because of pain in the line of incision. Morphine and atropine may both be used judiciously. Pain is not commonly a prominent postoperative symptom. Atropine is

a double-edged weapon, and while it may have a brilliant effect in the abolition of minor degrees of diffuse pulmonary moisture it is of little value in the presence of large amounts of bronchial secretion. The formation of a more viscid bronchial content may even defeat the purpose for which the drug is given.

The oxygen tent is the greatest single postoperative aid at the surgeon's disposal. It is used regularly for at least the first seventy-two hours and may be used longer as indicated. Dyspnea is not a prominent factor after pneumonectomy; nevertheless, the oxygen tent is helpful in prevention of postoperative pneumonia and serves to allay apprehension, because respiratory function is facilitated and deep breathing is not required.

The values for hemoglobin and red blood cells are the best index to the requirement for blood transfusions. In the presence of postoperative shock, nothing equals the transfusion of blood as a means of restoring and maintaining a proper blood pressure. A transfusion of 500 cc. may be given with impunity and repeated as indicated.

The surgeon who is able to depend on the cooperation of a competent bronchoscopist is fortunate. In the case in which operation was performed for suppurative disease, tracheal rhonchi were a prominent and foreboding feature, commencing forty-eight hours after the operation. Other methods of relief failing, it was decided to undertake tracheal (not bronchial) aspiration. This was successfully carried out with the patient in bed. He suffered no distress and had immediate relief from symptoms, although recurrence the following day required another aspiration. After the second aspiration, relief was permanent.

Whether to drain or not to drain the thoracic cavity after pneumonectomy depends on conditions noted at the time of operation. If dissection of the lung has been difficult and if capillary bleeding uncontrollable by ligature has occurred, it is well to drain. The amount of blood lost is under constant observation and the need for its replacement can be anticipated. If tube drainage is employed it is not necessary to displace dressings to aspirate the chest of a patient who may be very ill. A second indication for drainage is obvious contamination by pus or by bronchial secretion. Drainage is best obtained by insertion of a soft rubber tube through a stab wound independent of the operative incision. The tube is attached to a glass adapter, and another tube carries the contents of the pleural cavity into a bottle, the end of the tube being under water in the bottle. This device maintains a constant negative pressure in the pleural cavity. The preferable method is to close the chest without drainage, and this may be done if removal of the lung has been cleanly accomplished.

Of great value is the use of the portable x-ray apparatus in observing intrathoracic adjustments as they occur after operation. Serial roentgenograms furnish invaluable aid in the postoperative treatment, for physical signs following such an operation are difficult to interpret.

COMMENT

It has been repeatedly demonstrated[3] in experiments on dogs that total pneumonectomy is well tolerated, that recovery occurs in approximately 90 per cent of the animals operated on, that the occluded main stem bronchus will heal and remain closed and that absence of one lung is compatible with a long life and a useful existence. While most of the aforementioned facts have been found to hold equally true for patients who have been subjected to pneumonectomy, the recovery rate in the experimental laboratory is higher than that in the surgical theater. It must not be forgotten, however, that the animals operated on are in good health at the time of operation, while patients come to operation after having harbored malignant or suppurative disease or both for some time.

The age of the patient and the length of time the disease has been present are of great importance in the prognosis. It is found with experimental animals that the best results are obtained in those which have not yet attained full growth. Similarly, it is noted that children generally respond well to lobectomy and pneumonectomy. This is doubtless attributable to several factors. In children disease has not been harbored so long that adjacent structures are markedly affected by the morbid process, and general systemic effects are not pronounced. Furthermore, in children the elastic fibers of the remaining lung have lost none of their functional elasticity, whereas among adult patients loss of pulmonary elasticity is common. Nor is the thoracic cage as rigid in the child as in the adult. This rather pliant thoracic cage allows expansion of the sound remaining lung, and at the same time offers greater opportunity for a natural collapse of the chest wall on the side on which operation is done, tending to produce a thoracoplasty in effect without recourse to operation.

INDICATIONS FOR PNEUMONECTOMY

Total pneumonectomy is indicated as the treatment of choice for squamous cell carcinoma and adenocarcinoma of the bronchus and lung. For the former therapeutic roentgen rays are of no value. For adenocarcinoma the value of irradiation is questionable, and while an occasional patient appears benefited, recurrences are the rule rather than the exception, even when a beneficent result seems to have been obtained. Total pneumonectomy for malignant disease has not been

done for a sufficiently long time or in a sufficiently large group of cases to permit one to judge whether the operative results are better than those of irradiation.

Total pneumonectomy is also indicated for diffuse chronic suppurative disease of one or more lobes of the lung, such as may occur in the presence of bronchiectasis, cystic disease of the lung and multiple chronic pyogenic abscesses. The operation is requisite if the disease is limited either to one lung or to single lobes of both lungs. The use of this operation in the treatment of apparent unilateral tuberculous disease of the lung does not appear justified because of the risk of the operation, because of the fact that other, less formidable operations offer benefit to tuberculous patients and because postoperative involvement of the contralateral side is a real danger. The single exception to this rule occurs in the presence of complicating bronchial stenosis of a type that is not relievable by endoscopic methods. Patients with this condition become chronic invalids because they are subject to rather frequent attacks of pneumonitis and atelectasis caused by the stenosis of the bronchus. The stenosis may occur as a result of healing of an intrinsic bronchial infection or may be dependent on occlusive pressure on the bronchus from without, the usual cause of such pressure being the presence of enlarged hilar lymph nodes.

It is important for the surgeon to know what constitutes a suitable case for pneumonectomy. In the presence of malignant disease of the lungs it must first be established that the disease is primary in the lung and not metastatic to it from some other source. Painstaking physical and roentgenologic examinations are necessary. In the presence of a primary carcinoma of the lung, evidence of extension to some other organ is sufficient to contraindicate radical operation. Enlarged supraclavicular nodes particularly should be sought and if found should be subjected to biopsy. If carcinoma is found, palliative treatment with roentgen rays alone should be used.

In many cases of primary carcinoma of the lung it will be found possible to decide the question of operability only after exploratory thoracotomy has been done. The presence of enlarged glands at the hilus is in itself no contraindication to proceeding with the operation, unless these glands are obviously unresectable. Inseparable adhesions of the lung to the surrounding structures and extension of the growth across the carina are valid reasons for withdrawing from further operative intervention.

In the presence of diffuse suppurative disease of the lung or of bronchial stenosis the question of operability must depend in a large measure on the physical findings and on roentgen examination of the lung that will remain to carry on the respiratory function. Any marked

disease of this lung precludes pneumonectomy but not necessarily lobectomy. One may not be able to decide the question of operability until the chest has been opened, although the results of preoperative artificial pneumothorax or an attempted artificial pneumothorax may give some hint. In 2 patients (both adults) we have seen the operation of pneumonectomy abandoned after little headway had been gained in prolonged attempts to free the lung from its adhesions to the hilus and parietal pleura. In both patients it would have been foolhardy to proceed with the dissection. Both recovered from the exploratory thoracotomy.

SUMMARY

Two cases in which total pneumonectomy was done are reported, with comment on preoperative care, methods of anesthetization, operative technic, postoperative care and indications for operation. Factors influencing the success of total pneumonectomy are reviewed.

RETROPERITONEAL LYMPH NODES

THEIR IMPORTANCE IN CASES OF MALIGNANT TUMORS

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From the point of view of malignant tumors metastasizing through the lymphatic channels or spreading from one group of lymph nodes to another along the lymphatic channels the retroperitoneal nodes are the most important lymph nodes in the body. Perhaps they are not involved as frequently as are the cervical nodes, but, as far as the relative effect on the general condition of a patient suffering from a malignant process is concerned, the retroperitoneal nodes are far more important than any other group of nodes. Owing to their relative inaccessibility little attention has been given them, and the relation between certain clinical symptoms and physical signs and pathologic involvement of this group of nodes is often overlooked.

ANATOMY OF THE ABDOMINAL AND PELVIC NODES

From an anatomic standpoint most of the abdominal lymph nodes are retroperitoneal, in that none of them are within the peritoneal cavity. In this sense, while these nodes are situated within the general boundaries of the abdomen, they are all extraperitoneal, but it has become a custom to call them retroperitoneal, and usage has established this expression.

The abdominal and pelvic lymph nodes form a continuous system, but for purposes of description they may be divided into two main groups: (1) the iliac nodes and (2) the abdominoaortic nodes. The second group of abdominoaortic nodes may be subdivided into: (1) the mesenteric group and (2) the para-aortic or, as it is sometimes called, the juxta-aortic group. The nodes which form these groups are all connected by lymph channels, and other channels bring to different parts of this extensive system of nodes lymph from the lower extremities and from all the organs and structures in the pelvis and abdomen. Lymph which has passed through these nodes passes thence mainly through the thoracic duct into the subclavian vein, but some of it passes upward through channels which connect the upper para-aortic nodes with similar nodes which follow the course of the aorta on the left side and of the inferior vena cava on the right side.

Below the bifurcation of the common iliac vessels the iliac nodes are made up of two chains : (1) the external iliac nodes and (2) the internal iliac nodes. Above the point of junction of the external and internal iliac vessels the iliac nodes consist of a single chain of nodes accompanying the common iliac vessels to the bifurcation of the abdominal aorta and the inferior vena cava. The two chains of common iliac nodes then come together to form the para-aortic nodes.

The external iliac nodes receive lymph from the superficial iliac nodes, the deep iliac nodes, the lower extremities, the glans penis or the clitoris, the umbilicus, the lower part of the abdominal wall, the upper part of the vagina, the neck of the uterus, the prostate gland, the bladder, the membranous portion of the urethra and the internal iliac nodes. All this lymph then passes through direct channels communicating with the common iliac nodes and thence to the para-aortic nodes.

From the perineum, the main part of the urethra, the deep tissues of the posterior aspect of the thigh and the buttocks and the pelvic organs lymph passes along channels and through primary nodes along the anterior aspect of the sacrum and the middle hemorrhoidal vessels into the internal iliac nodes which accompany the internal iliac artery. Lymphatic channels communicating with the common iliac nodes then convey the lymph to these nodes, where it joins with lymph from the external iliac nodes; from the common iliac nodes other lymphatics convey the lymph to the para-aortic nodes.

The para-aortic nodes, numbering twenty-five to thirty (fig. 1), follow the course of the abdominal aorta and the inferior vena cava. Some of the nodes are on the right of these vessels, some on the left, some in front and some behind. All are rather large. Into the right para-aortic nodes flows lymph from the right common iliac nodes, the right testis or ovary, the right half of the uterus, the right fallopian tube and broad ligament, the right kidney and adrenal gland and nodes which accompany the lumbar arteries. Through communicating channels lymph may pass from the right para-aortic nodes to the nodes behind or in front of the abdominal aorta and to the receptaculum chyli. Into the left para-aortic nodes flows lymph from the corresponding organs and structures on the left side of the body.

Into the same group of nodes, especially those above the point of origin of the spermatic or ovarian vessels, a series of lymphatic channels on each side bring lymph directly from the right or left testis or ovary. These channels follow the course of the spermatic arteries in the male or of the ovarian arteries in the female. This explains why a malignant tumor of the testis or ovary which has not ruptured the capsule of the organ metastasizes first to these nodes. Metastasis to the inguinal nodes is a sign that the neoplasm of the testis or ovary has ruptured the capsule or that the lymphatics of the organ have an anomalous

arrangement. In the presence of tumor of the ovary rupture of the capsule is common, and owing to the situation of the organ this leads to rapid extension of the malignant process to the peritoneum and to other abdominal organs. This is not often true of tumor of the testis.

The anterior para-aortic nodes are situated in front of the abdominal aorta; some are at the point of origin of the inferior mesenteric artery, some are at the point of origin of the superior mesenteric artery, and some form an important group around the celiac axis. The group of nodes in the region of the celiac axis is situated behind the stomach
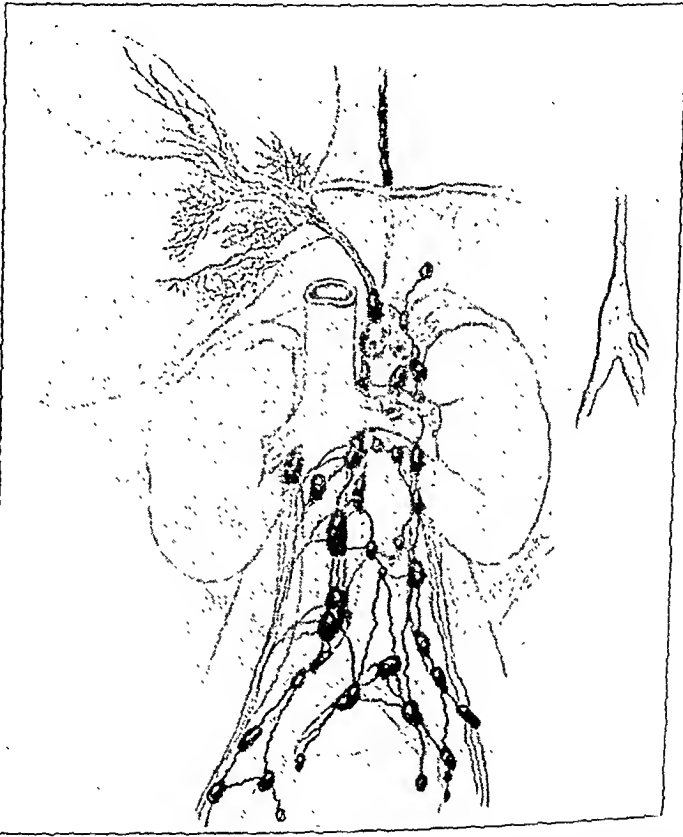
Fig. 1.—Para-aortic and iliac lymph nodes, into and through which flows lymph from the lower extremities, pelvis, pelvic organs, buttocks, small and large intestine, stomach, liver, kidneys, adrenal glands and spleen. The lymph from the testes or ovaries is carried through separate lymph channels directly into the upper para-aortic nodes in the region of the celiac axis.

and in close relation to the pancreas. Lymphatic channels carry lymph from the anterior nodes to the right and left para-aortic nodes, to the posterior nodes and to the receptaculum chyli. Other channels bring to the para-aortic nodes lymph from the stomach, intestines, liver, pancreas and spleen.

Along the greater part of the rectum, the descending colon and the splenic flexure (fig. 2) and along the branches of the inferior mesenteric

artery which supply these structures are situated nodes connected by lymphatic channels which unite to form larger and larger channels and through which lymph flows into the para-aortic nodes. Other nodes and channels which form part of the same extensive system are situated along the transverse and ascending portions of the colon, including the cecum and appendix, and along the entire length of the small intestine (fig. 3). Thence, following the branches of the superior mesenteric artery, they also convey lymph to the para-aortic nodes.

Fig. 2.—Lymphatic drainage of the rectum, descending colon and splenic flexure. Lymph from these structures is carried to the para-aortic lymph nodes.

Along the lesser and the greater curvature of the stomach, where they follow the course of the gastric or gastroepiploic arteries, are situated a series of nodes into which flows lymph from the superficial and deep coats of the organ. Through secondary communicating channels the lymph then passes into the group of para-aortic nodes in the region of the celiac axis. The lymphatic channels which drain the fundus of the stomach pass toward the left side and convey lymph to the splenic

nodes. Situated between the spleen and the pancreas and collecting
lymph from both of these organs as well as from the fundus of the
stomach, the splenic nodes follow the course of the splenic artery and
also convey lymph to the para-aortic nodes. Following the course of
the hepatic artery, of the portal vein, of the right gastroepiploic artery
and of the cystic and common bile ducts, a series of nodes and com-
municating channels collect lymph from the liver and convey it to the
upper or celiac group of para-aortic nodes.
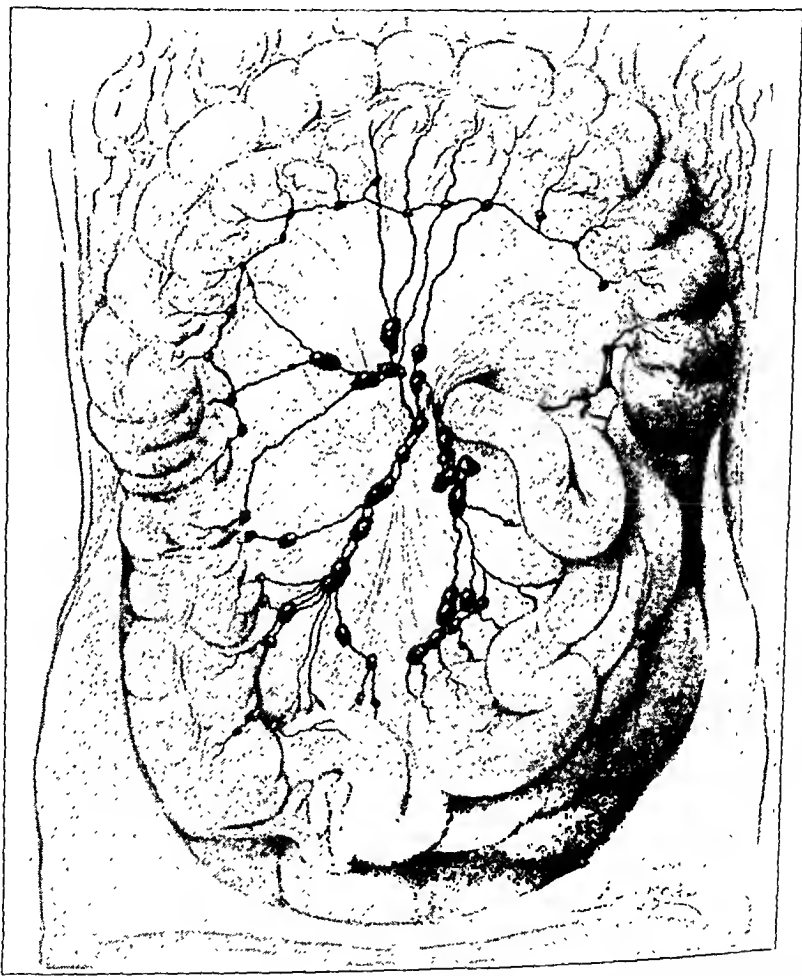
Fig. 3.—Lymphatic drainage of the small intestine, vermiform appendix and
ascending and transverse portions of the colon. The lymph from these structures
also is carried to the para-aortic nodes.

Besides these main groups of lymph stations, each abdominal organ
has its own system of lymph channels and nodes through which the
lymph passes on its way to the main collecting nodes in the para-aortic
group. To attempt to describe in detail the lymphatic system of each
organ would be to divert the attention of the reader from the main
subject of this paper. What is essential to remember is that practically

all the lymph from the abdominal and pelvic organs. as well as from the lower extremities, must pass through the para-aortic nodes or through both the mesenteric and the para-aortic nodes. Casual reflection alone is sufficient to make one realize that groups of lymph nodes which drain so many important organs in the abdomen and pelvis must themselves be relatively important.

METASTASIS FROM CARCINOMA

Carcinoma of the bladder, prostate gland, uterus or rectum often extends backward (or outward and backward) along the lateral and posterior planes of the pelvis, where the main lymphatic channels and nodes are situated, frequently causing a dull aching pain in the sacral region. The malignant process may infiltrate some of the sacral nerves;[1] when this occurs the pain becomes much more severe. Not infrequently. especially in carcinoma of the prostate gland, the malignant elements find their way into the blood stream and thence to various bones or internal organs. The symptoms caused by the primary growth continue to increase, but to these are added the symptoms caused by extension of the tumor beyond the organ primarily affected.

Many patients who are known to suffer from carcinoma of the bladder, prostate gland, uterus or rectum or who have previously undergone partial or complete surgical resection of one or another of the organs mentioned consult a physician because for some time they have been distressed by fresh symptoms. These symptoms may be: pain in the back, pain in the abdomen, bloating and belching after meals, abdominal distention, increase in flatus, a sensation of undue fulness after eating (which the patients often describe as a sense of not having enough space for food), gradual increase in size of the abdomen or increasing constipation.

Backache.—In most cases the backache affects the lumbar region, but sometimes the sacral or the lower part of the thoracic region also is affected. In certain cases backache is absent but the patient complains of pain around one hip and down the corresponding thigh, around the knee or throughout the lower extremity. Sometimes the pain is felt chiefly, if not wholly, in one or both feet and only later extends to the knee, thigh or hip. Not infrequently the condition is mistaken for sciatic neuritis or sciatica. and the patient may be treated on this basis for some time, with little or no success. Pain in the lumbar region may not manifest itself for some time. The pain, which usually is a dull ache, often extends to one or both hips and down one or both lower extremities. Sometimes it gradually assumes a boring character: it may become so severe as to require opiates for relief.

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1. Elaut. L.: The Surgical Anatomy of the So-Called Presacral Nerve. Surg., Gynec. & Obst. 55:581-589 (Nov.) 1932.

When the pain is dull, roentgenographic examination of the spine and pelvis may not give the slightest indication of metastasis to these bony structures. Under these circumstances the patient's symptoms are probably due to metastasis of the tumor to the para-aortic lymph nodes or to these and the mesenteric nodes, and this possibility should always be kept in mind. The pain is probably due to the pressure of nodes enlarged by metastasis on nerves that enter into the formation of the lumbosacral plexus or on branches of this plexus which supply the hips and lower extremities. In favor of this view is the fact that suitable exposure of the lower part of the thoracic region and of the lumbar and sacral regions to converging beams of roentgen rays is often followed by partial or complete relief from pain, and the relief thus obtained may continue for weeks or months. Moreover, the degree of relief following irradiation is likely to be greater when the backache is dull than when it is severe and boring.

When the pain in the back is severe or boring, a roentgenogram of the spine and pelvis is likely to yield evidence of skeletal metastasis. Should this be absent, severe backache, with or without extension of the pain to one or both lower extremities, may be due to metastatic infiltration of the aforementioned nerves. In this event the prospect of relief from pain after roentgen treatment depends on the kind of tumor and its sensitiveness to irradiation and on how much the nerves have been injured. If the nerves have been injured beyond repair, an indication of the fact may be found in the complete lack of response to irradiation. If the neural injury has been only partial, roentgen treatment is likely to be followed by some degree of relief.

One factor which may have considerable influence on the action of roentgen irradiation is the site of the injury in relation to the region treated. Even when the pain is confined to the hip or the lower extremity (assuming that metastasis to the pelvic bones or to the bones of the extremity has been carefully excluded by roentgenographic examination), treatment directed to the hip or to any part of the extremity is not likely to have any effect on the pain. The treatment should be directed mainly to the lumbar region, but the lower part of the thoracic region and the sacroiliac region also should be irradiated.

Pain in the Abdomen.—When pain in the abdomen is the chief complaint, it usually assumes one of two forms; in one form the pain recurs at irregular intervals, tends to be slight or moderate at first, gradually increases in intensity for a variable period and then gradually subsides. It may last only a few minutes or may continue for a longer time, and it may recur at varying intervals. It often shifts from one part of the abdomen to another, but in some cases this tendency to shift is not a prominent feature. Week by week the pain increases in severity

and constancy. It is often associated with gradually increasing constipation. The impression is that of a spastic pain, probably caused by mechanical interference with the motor function of the bowel by gradual enlargement of the para-aortic nodes and perhaps also of the mesenteric nodes. The variations in the pain and in the other intestinal symptoms observed in different cases probably depend on variations in the anatomic relation between the nodes and the intestine, according to the particular nodes most involved and the part of the intestine affected.

The other form of pain occurs more or less regularly after meals and may thus suggest peptic ulcer. Intermittent at first, it gradually becomes more constant and is often accompanied by a sense of epigastric fulness after eating. As time goes on, the patient, in an effort to reduce the discomfort or pain caused by an ordinary meal, may acquire the habit of taking food in small quantities at frequent intervals. The pain, which may be a dull ache or soreness, is sometimes accompanied by nausea and vomiting.

Bloating and Belching—Flatus.—Bloating and belching after meals are common symptoms and are usually associated with the aforementioned sense of fulness in the epigastrium after eating. These symptoms gradually increase and are undoubtedly caused by crowding of the stomach and upper part of the small intestine by enlarging retroperitoneal nodes. The stomach and intestine can no longer expand as their contents increase; interference with peristaltic action probably causes abnormal delay in the emptying of the stomach and in the transit of food and gas through the upper part of the small bowel, and gas tends to accumulate. In some cases a gradual increase in flatus indicates interference with the normal function of the lower part of the small intestine and colon by mechanical pressure of nodes enlarged by metastasis of the tumor along the lower half of the abdominal aorta and sometimes also of the iliac nodes.

Enlargement of Abdomen.—An occasional patient complains of a gradual increase in size of the abdomen and is obliged to wear clothing of a larger size. Usually this enlargement of the abdomen is accompanied by bloating, belching and a sensation of undue fulness, weight and discomfort in the epigastrium, especially after eating.

Constipation.—Constipation is such a common complaint of persons who are otherwise well that little weight could ordinarily be attached to this widely prevalent disturbance by itself. However, when a person who is known to have had a malignant process and who previously has seldom or never been affected by sluggishness of the colon complains that for several weeks or months there has been a gradually increasing disinclination of the large bowel to evacuate its contents, it seems justifiable to suspect a mechanical cause. Moreover, when, as not infrequently

occurs, roentgen irradiation of the abdomen is shortly followed by recovery of normal intestinal function for weeks or months, the suspicion seems confirmed.

Physical Signs.—When a carcinoma of the bladder, prostate gland, uterus or rectum has invaded the retroperitoneal nodes, the physical signs may be so overshadowed or masked by those caused by the primary tumor or by extension of the growth to the abdominal structures and organs that a clear distinction between them may be difficult or impossible. Also when the primary neoplasm has been removed surgically and the symptoms mentioned arise later, the presence of local recurrence, with or without extension to various abdominal structures, may add a confusing note. In general, the physical signs related to the primary tumor or to local recurrence of the malignant process after an antecedent excision are rather definite. Confusion arises chiefly when metastasis to the peritoneum, intestine or liver has developed. Even though the physical signs are sometimes not clear enough to enable one to exclude metastasis to the liver, for example, they may be sufficient to indicate that the retroperitoneal nodes also are probably involved.

When the primary growth has been removed surgically and clinical evidence of local recurrence is lacking, the following physical signs increase the probability of metastasis to the para-aortic nodes:

Palpation in the epigastric and umbilical regions (and sometimes in the hypochondriac and lumbar regions as well) elicits a sensation of abnormal resistance. When the abdominal wall is obese or muscular or when the abdomen is distended with gas or fluid, perception of this abnormal resistance may be difficult. In the majority of cases, however, recognition of abnormal resistance offers little difficulty. Sometimes the resistance is greater on one side than on the other, and sometimes its distribution is fairly uniform. Sometimes it is confined to the upper half of the abdomen, and sometimes it extends downward as far as the iliac regions. In some cases a sensation of irregular nodules is obtained, but in others the resistance is diffuse and uniform. Moreover, the impression derived by palpation is that this abnormal resistance is rather deep. Usually the lower border of the liver, which falls and rises with respiration, can be distinguished clearly, but occasionally the retroperitoneal nodes are so large and closely packed and extend so far forward and upward that it may be difficult or impossible to be certain where the liver ends and the nodes begin. The same difficulty may arise when the liver also has been invaded by metastasis. When the para-aortic nodes are only slightly affected the sensation of deep resistance may be correspondingly slight and may be obtainable only by deep palpation on each side of the spine.

The second significant sign is slight or moderate tenderness when pressure is exerted on the deep resistance already described. Usually

this tenderness, while seldom pronounced, is definite and cannot be mistaken for the discomfort caused by pressure of the examiner's hand. Few patients have any difficulty in distinguishing between the two. When abnormal resistance is present and pressure is exerted, the patient says, "That hurts," winces or tries to draw away. When the abdomen is normal, on the contrary, the anterior abdominal wall can be depressed until it comes in contact with the great vessels and the spine, and the patient's only sensation is discomfort from the pressure.

TUMORS OF THE TESTIS OR OVARY

Lymph from the testes or ovaries normally drains not into the inguinal nodes but (through a separate system of lymphatic channels) directly into the upper para-aortic nodes. From this point the lymph may pass upward through the thoracic duct and empty into the subclavian vein on the left side, or on the right side (when a right lymphatic trunk is present) into the junction of the internal jugular and the subclavian vein. A tumor of the testis never metastasizes to the inguinal nodes unless it has perforated the capsule of the organ; in fact, extension of a malignant process from the testis to the inguinal nodes is an absolute sign that the tumor has broken through the capsule of the organ. In some cases of testicular tumor, metastasis to the para-aortic nodes may be accompanied or followed by metastatic invasion of the iliac nodes without involvement of the inguinal nodes. As the experimental studies of Jamieson and Dobson [2] have shown, this may be due to such effective blocking of the malignant process by the para-aortic nodes that the malignant elements are dammed back into the iliac nodes either through the usual channels or through collateral channels.

The most common malignant neoplasms of the testis, the embryonal carcinoma (or seminoma) and the mixed. or teratoid, tumor, are characterized by early metastasis—much earlier than is generally suspected. Moreover, the first site of metastasis from a tumor of this kind is almost always the para-aortic nodes, especially those above the point of origin of the spermatic or ovarian vessels. Later the malignant process may find its way through the thoracic duct to the so-called sentinel nodes in the supraclavicular region, may block the thoracic duct in the mediastinum and may thence spread outward to invade the lungs; or, having succeeded in running the lymphatic blockade of the para-aortic and sentinel nodes. the malignant cells may be thrown into the circulation and be scattered through the lungs, the brain or other organs. In many cases. however. the blockade offered by the para-aortic nodes prevents further dissemination of malignant cells for many months or for several years.

2. Jamieson, J. K., and Dobson, J. F.: The Lymphatics of the Testicle, Lancet **1**:493–495 (Feb. 19) 1910.

Symptoms.—Metastasis to the para-aortic nodes is prone to give rise sooner or later to some of the symptoms which have already been described in connection with carcinoma of the bladder, prostate gland, uterus or rectum, and the gradual development of these symptoms should always make one consider the possibility of metastasis to the retroperitoneal nodes, which are the first station of drainage for lymph from the testis.

The same is often true of certain types of tumor of the ovary, but the tendency of many ovarian neoplasms to rupture the capsule of the organ and to spread over the peritoneum, where the malignant elements form innumerable implants or cause the omentum and coils of intestine to adhere to one another or to the pelvic structures, tends to confuse the clinical picture. Under these conditions, also, the prevalence of ascites adds another confusing factor.

Therefore, whenever a patient who is known to harbor a malignant tumor of the testis (or ovary) or to have had such a tumor removed a few weeks or months previously begins to complain of some of the symptoms mentioned, the possibility of metastasis to the para-aortic nodes should always be considered. To overlook this possibility may be to rob the patient of months or years of life, to throw away the slight chance of a permanent cure or at least to deprive the patient of the partial or complete relief from pain and other symptoms which might readily be obtained by proper roentgen therapy. Too often, unfortunately, the factors responsible for the symptoms are not recognized, and their significance is overlooked until physical deterioration has progressed beyond even temporary salvage.

Physical Signs of Retroperitoneal Metastasis of Tumors of the Testis. —When the para-aortic lymph nodes have been invaded by metastasis from a tumor of the testis, the physical signs at first may be as slight and vague as the symptoms. As the nodes enlarge, however, they gradually form a mass, the greater portion of which is on the same side as the primary growth in the testis. It usually is situated in the epigastric and the upper part of the umbilical region, and more than half of it is to the right or left of the median line, according to the testis primarily involved. In some cases the metastatic growth may extend downward into the iliac region on the same side; this occurs when the lower para-aortic and the common iliac nodes also have been invaded, but almost always this follows metastasis to the upper group of para-aortic nodes.

When a definite mass cannot be palpated, a sensation of deep abnormal resistance can usually be felt, and pressure on this resistance elicits tenderness, which is usually slight or moderate. When these

physical signs are associated with the symptoms previously described, metastasis to the retroperitoneal lymph nodes may be assumed as probable.

When the distinct sensation of a mass is obtained, the mass may be nodular or fairly smooth; this probably depends on how closely packed the enlarged nodes are. Rather firm, the mass as a rule is fixed and immovable, but sometimes a slight degree of mobility may be perceived. Regardless of its consistency or mobility, however, pressure on the mass can be counted on to elicit a slight degree of tenderness. When the mass is situated mainly in the epigastric and the upper umbilical region on the left side, it may extend into the left hypochondriac region and may easily lead one to mistake it for an enlarged spleen or kidney. Such an error is far from rare. When, on the contrary, the bulk of the mass lies to the right of the median line, it is frequently mistaken for an enlarged liver. Of course, metastasis to the liver may occur in a case of this kind, but this is usually a late manifestation. Moreover, metastasis to the liver is relatively uncommon; the lungs are much more likely to be invaded. Careful palpation and percussion, with the abdomen relaxed as much as possible, generally enable one to distinguish between retroperitoneal nodes enlarged by metastasis from a tumor and an enlarged spleen, kidney or liver, especially if the great frequency of metastasis to the para-aortic nodes is kept in mind.

Another physical sign which may sometimes be found is moderate tenderness to deep palpation in the lumbar portion of the back, on each side of the spine, in the ninth, tenth or eleventh intercostal space and sometimes below the ribs. In this connection it is perhaps significant that the tenderness elicited by pressure along the lower part of the thoracic portion and the lumbar portion of the spine impresses the patient as having the same quality as the tenderness obtained by deep palpation through the anterior abdominal wall.

Physical Signs of Retroperitoneal Metastasis from Tumors of the Ovary.—These are the same as the signs described in the foregoing section, but frequently they are so masked by other signs (and symptoms) produced by more or less extensive dissemination of malignant elements to the peritoneum and other structures anterior to the para-aortic nodes that it is often difficult or impossible to recognize retroperitoneal metastasis with any degree of assurance. In some cases, nevertheless, the symptoms and physical signs may strongly suggest the possibility, and it is important to bear it in mind because if the pain is due largely or wholly to retroperitoneal metastasis, a considerable measure of relief may be afforded by roentgen treatment; this is possible, however, only when treatment is directed to the structures responsible for the pain. Indiscriminate irradiation of the abdomen, hip or lower extremity is not likely to have much, if any, favorable effect.

In many cases, unfortunately, a malignant tumor of the ovary has the character of cystadenoma or adenocarcinoma, a prominent complication of which is ascites, and this often makes palpation of the abdomen unsatisfactory. In other cases the bowel may be so distended with gas that all other physical signs are partly or completely obliterated.

LYMPHOBLASTOMA (HODGKIN'S DISEASE OR LYMPHOSARCOMA)

Important as metastasis to the para-aortic nodes or to both the para-aortic and mesenteric nodes often is in the presence of tumor of the bladder, prostate gland, rectum, uterus, testis or ovary, involvement of these nodes is still more important in Hodgkin's disease or lymphosarcoma. It is generally taken for granted that this type of disease, or, rather, this variety of tumor,[3] always begins in the cervical nodes and thence gradually extends to other groups of nodes. This is far from true. In a considerable proportion of cases the malignant process first affects the retroperitoneal nodes and gradually spreads to the nodes in other regions. But even when the neoplastic process has its origin in the cervical or the mediastinal nodes it almost invariably reaches the retroperitoneal nodes sooner or later. The time required for this transfer of malignant elements from the cervical to the retroperitoneal nodes may vary from a few months to several years. In some cases in which the pathologic process has apparently started in the retroperitoneal nodes, slight or moderate symptoms have been present for a long time before the patient is impelled to seek relief. The onset of symptoms is usually insidious and gradual; pain often either is absent or is moderate, inconstant or interrupted by more or less prolonged remissions, so that many patients bear with their distress for months or

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3. From a clinical standpoint, at least, so-called Hodgkin's disease, as well as lymphosarcoma, is undoubtedly a malignant process or a variety of a malignant process affecting the lymph nodes and sometimes all the lymphoid structures in the body. If, as Furth and his co-workers have shown, leukemia in animals is a form of malignant disease, there would seem to be little ground for excluding from the same category Hodgkin's disease and lymphosarcoma (Furth, J.: Studies on the Nature of the Agent Transmitting Leucosis of Fowls: III. Resistance to Desiccation, to Glycerin, to Freezing and Thawing; Survival at Ice Box and Incubator Temperatures, J. Exper. Med. **55**:495-504 [March] 1932; Transmission of Myeloid Leukemia in Mice, Proc. Soc. Exper. Biol. & Med. **31**:923-925 [May] 1934; Transmission of Myeloid Leukemia of Mice: Its Relation to Myeloma, J. Exper. Med. **61**:423-445 [March] 1935. Furth, J., and Miller, H. K.: Studies on the Nature of the Agent Transmitting Leucosis of Fowls: II. Filtration of Leucemic Plasma, ibid. **55**:479-493 [March] 1932. Furth, J.; Seibold, H. R., and Rathbone, R. R.: Experimental Studies on Lymphomatosis of Mice, Am. J. Cancer **19**:521-604 [Nov.] 1933. Furth, J., and Strumia, M.: Studies on Transmissible Lymphoid Leucemia of Mice, J. Exper. Med. **53**:715-731 [May] 1931).

years before seeking to know the cause and have it removed. Unfortunately, the frequency of primary or secondary involvement of the para-aortic or mesenteric nodes is so seldom realized that the factors responsible for the patient's symptoms frequently go unrecognized for a long time or are regarded as representing a merely functional disturbance.

A striking feature is the great variety of the symptoms, and this perhaps more than anything else accounts for the difficulty which those who have not examined and followed a large number of patients with the disease have in recognizing the character and the cause of the patient's difficulties. One patient may complain chiefly or wholly of impairment of vision, thickening of the lids or bulging of the periocular tissues; another may complain of pain in the right upper quadrant or the right lower quadrant of the abdomen and may already have undergone cholecystectomy or appendectomy, with only temporary relief; another patient's chief or only complaint may be of itching which, having been confined for a time to the lower or upper extremities, has gradually extended to the entire body and has become so severe that restful sleep has become impossible; the principal difficulty of another patient may be pain in the back, radiating to one or both lower extremities; another may have as his chief or only symptom an "afternoon fever," which may be continuous or may occur in intermittent waves; another may suffer mainly from pain in the "stomach" occurring from one-half to three hours after meals; the chief complaint of another may be a progressive and unaccountable loss of weight; another may complain only of amenorrhea. And yet all these patients may be suffering from Hodgkin's disease or lymphosarcoma affecting the retroperitoneal nodes only or involving these and groups of nodes in other regions as well.

By the great variation in the symptoms and by the protean complications which may develop during their course, Hodgkin's disease and lymphosarcoma can simulate many diseases. So true is this that, as experience accumulates, an increasing proportion of the puzzling conditions which baffle physicians prove to be lymphoblastoma, and in many such cases the malignant process has apparently originated in the retroperitoneal nodes.

Before considering the individual symptoms I should like to point out that the history, if carefully taken, may often be sufficient to indicate the character of the pathologic process or to raise a strong suspicion of it. Moreover, when both the history and the physical findings point to lymphoblastoma, an accurate diagnosis can be made in a large percentage of cases without benefit of biopsy. In some cases, indeed, reliance on the results of the microscopic examination of an excised lymph node

may lead one astray. Not only in the first node excised but sometimes in three different nodes successively removed from the same region or from different regions may the pathologist be unable to find anything but inflammatory changes. In such cases a pathologic report of "inflammatory changes" should be regarded as a negative finding and investigation should be continued as if biopsy had not been done; that is, when the history and physical findings point strongly to lymphoblastoma, a finding of "inflammatory changes" should be disregarded, and the clinician should rely on the clinical features and the physical findings.

Occasionally the most experienced pathologist may have difficulty in distinguishing between a highly malignant epithelial cell tumor and Hodgkin's disease or lymphosarcoma and may report "squamous cell epithelioma of grade 4 malignancy" or even "adenocarcinoma" when both the history and the distribution of the lymphadenopathy are inconsistent with such a diagnosis. Sometimes, of course, the history and the physical findings are not entirely conclusive, but when they are the pathologic interpretation should be discarded as probably misleading or at least should not be allowed to outweigh all other evidence. Too often, when the clinician receives the report of a pathologist, he stops thinking and allows his judgment to lapse. The clinical and physical features of a case may point more accurately to the correct diagnosis than the microscopic changes.

To attempt to distinguish between Hodgkin's disease and lymphosarcoma by clinical features alone is to attempt the impossible. In the average case the two conditions are identical not only in their clinical manifestations, but also in their response to treatment. Not a single symptom or physical sign can be taken as a clearly distinctive feature. Therefore, any attempt to make such a distinction on clinical grounds is only a guess. Even microscopic examination is not free from difficulties in this respect, if one is to judge by the frequent inability of different pathologists to agree in their interpretations of tissue changes as representing Hodgkin's disease or lymphosarcoma. For these reasons it is desirable to avoid a distinction surrounded by such difficulties and uncertainties and to group both conditions under the collective term "lymphoblastoma." Clinicians, at least, might well do so.

Symptoms.—A common feature of the symptoms occurring in cases in which the retroperitoneal nodes are primarily or secondarily affected by lymphoblastoma is that they often vary considerably in degree from time to time. Treatment of different kinds may be followed by partial or complete remission of symptoms. For example, after cholecystectomy or appendectomy performed on the unfounded assumption that the abdominal pain was due to cholecystitis or to appendicitis the pain may diminish greatly or disappear, and the general condition may improve

considerably for weeks or months, only to return later. Simple medical treatment may be followed by temporary improvement, and even without any treatment the symptoms may subside and may be slight or absent altogether for a time.

Usually the extent of the condition roughly parallels the stage of its evolution or the point in its course, but exceptions are not uncommon. Sometimes the lymphoblastoma may have invaded nearly all the lymph nodes in the body and the patient may appear to be near death; the nodes in different regions may have enlarged enormously and may be causing more or less pronounced symptoms of pressure. Yet careful treatment with roentgen rays may cause rapid and marked regression of the lymphadenopathic masses and corresponding improvement in the symptoms, and if the treatment is properly followed and the patient kept under close observation life may be prolonged for many months or even for several years.

An idea widely held is that persons suffering from Hodgkin's disease or lymphosarcoma cannot be expected to live more than two or three years. This is true in a considerable proportion of cases, but many patients may live five, ten, fifteen and even twenty or more years. The two main factors which influence survival are: (1) the relative acuteness or chronicity of the disease in the individual case and (2) the quality of the treatment. Of these two factors the first is much more important than the second.

Lymphadenopathy.—A common feature is that the size of the enlarged lymph nodes often varies considerably from time to time, irrespective of treatment. Many patients suffering from Hodgkin's disease or lymphosarcoma are abnormally subject to infection of the respiratory tract. In the course of each infection of this kind or soon afterward the affected nodes tend to enlarge more or less rapidly for a time. Later the swelling may subside again, but it seldom disappears, although the patient may no longer be aware of its presence. In most cases of lymphoblastomatous invasion of the retroperitoneal nodes the patient is not aware of masses, lumps or tumors in the abdomen. Occasionally, however, the patient may have discovered a mass and may tell the physician that some weeks or months later the mass disappeared. Such a statement should never be accepted at face value. What it usually means is that the mass diminished until the patient could no longer feel it.

A true tumor of this or any other kind rarely disappears spontaneously. Sooner or later its further growth becomes manifest. While in most cases the tendency of the affected nodes is to increase in size until they attain considerable proportions, some cases are encountered in which the lymph nodes remain small throughout the course of the malignant process. The mere size of the nodes, therefore, cannot be taken as an indication of the stage of the process.

In relation to its importance, altogether too much attention is given to enlargement of the cervical, axillary and inguinal nodes. With a few exceptions, enlargement of these nodes never affects the general health of the patient. When general health has deteriorated, the lympho-blastomatous process has almost always invaded the nasopharynx, the tonsil or pharynx, the mediastinal nodes, the retroperitoneal nodes or the lymphoid tissue or lymph nodes in all four of the regions mentioned. When the nasopharynx, tonsil or pharynx is extensively involved, this may cause mechanical interference with respiration or deglutition. Similar difficulties may arise from enlargement of the mediastinal nodes. Occasionally, enlarged mediastinal nodes may cause circulatory embarrassment. In point of frequency as well as of relative importance, however, a deleterious influence on the general condition of the patient is much more likely to follow invasion of the retroperitoneal nodes than involvement of the mediastinal nodes or of the nasopharynx, tonsil or pharynx.

In general, involvement of the axillary or inguinal nodes, and especially of the latter, does not occur until the para-aortic nodes have been affected for some time. Therefore, except in the few cases in which the malignant process has originated in the inguinal nodes, enlargement of these nodes from lymphoblastomatous hyperplasia is usually associated with involvement of the retroperitoneal nodes and should cause one to suspect such involvement. Invasion of the axillary nodes does not have the same significance, but it may occur in association with lympho-blastoma affecting either the retroperitoneal or the mediastinal nodes. Rarely, the process may begin in the axillary nodes and may gradually spread from these to the nodes in other regions.

Secondary involvement of the retroperitoneal nodes in cases in which the lymphoblastomatous process has begun in some other region (cervical, mediastinal or inguinal) renders the prognosis more unfavorable. While the affected retroperitoneal nodes may retrogress and the related symptoms may abate or disappear after irradiation, prolonged control of the lymphadenopathy is more difficult to achieve than in the case of cervical, mediastinal or inguinal adenopathy. Moreover, roentgen or radium irradiation of the retroperitoneal nodes involves exposure of other comparatively sensitive structures, such as the small intestine and spleen, as well as of a large quantity of blood. A common result is more or less pronounced leukopenia, which, though usually temporary, may continue for weeks or months and may interfere with systematic treatment.

Loss of Strength.—Perhaps the most common symptom mentioned by patients suffering from lymphomatous invasion of the retroperitoneal nodes is a loss of strength, which is often expressed as "tiring easily."

"loss of endurance" or "loss of pep." A man or woman who previously has been able to work steadily without undue fatigue finds it increasingly difficult to carry on as of old and complains of "being tired all the time," and this has nothing to do with the age of the patient or with his condition in other respects. A patient may not have any other symptoms for a long time and may not be aware that he is ill. Often this symptom is disregarded by the physician, who does not realize its significance or who, not finding evidence of any organic disturbance, may diagnose the patient's condition as neurasthenia.

When a patient known to be suffering from Hodgkin's disease or lymphosarcoma begins to complain of "feeling tired all the time," it may be taken almost for granted that the para-aortic nodes and perhaps also the mesenteric nodes have been invaded by the lymphoblastomatous process.

When a patient who is not known to be suffering from Hodgkin's disease or lymphosarcoma begins to complain of "feeling tired all the time," the possibility of lymphoblastoma should always be considered. If enlarged lymph nodes are found in other regions or if other symptoms of primary or secondary invasion of the para-aortic or mesenteric nodes are present the possibility becomes a probability or a certainty.

Loss of Weight.—When they first consult a physician, and often for a long time afterward, many patients affected by Hodgkin's disease or lymphosarcoma maintain their weight at or near the normal level. In many cases, therefore, loss of weight is not included among the patient's symptoms. Sometimes this is a significant feature in the differential diagnosis. For example, when symptoms pointing to an abdominal tumor have been present from one to five years, with little or only slight and gradual increase, and when the patient's weight and general condition are much better than would be expected the tumor is likely to be a lymphoblastoma rather than a carcinoma.

In other cases loss of weight, sometimes unaccountable, is a prominent symptom or the principal symptom. A patient may lose from 20 to 40 pounds (9 to 18 Kg.) in from two to six months, and it may be this alone which brings him to consult a physician. Such a complaint should always lead to a thorough investigation of the gastrointestinal tract and of the abdominal and pelvic structures generally. If evidence of an intrinsic. organic lesion as an adequate cause cannot be demonstrated and especially if one or more tumors extrinsic to the stomach, intestine or kidney are revealed by roentgenologic examination the possibility of primary or secondary lymphoblastoma of the retroperitoneal nodes should always be considered.

A curious circumstance is that the decrease in weight may occur in spite of a normal or ravenous appetite and a seemingly adequate intake

of food. Apparently the disturbance affects the absorption of foodstuffs or of essential vitamins by the small intestine.

Pain in the Abdomen.—In Hodgkin's disease and lymphosarcoma enlargement of the lymph nodes in regions other than the abdomen usually is not accompanied by pain. Sometimes the nodes may be slightly or moderately tender for a time, but this is seldom a prominent feature. Moreover, as time goes on, even the slight initial tenderness tends to diminish or disappear. It is precisely because of this common painlessness of the enlarged nodes that so many patients allow them to continue to enlarge for a long time before seeking medical attention. In fact, this absence of pain or tenderness often constitutes a valuable point of differentiation. Although not themselves tender, the lymph nodes may sometimes grow to such proportions as to cause more or less discomfort.

In general, this is as true of the retroperitoneal nodes as of the nodes in other regions. For many weeks or months, in many cases, the sensory disturbances are hardly sufficient to be designated as pain. However, as the malignant process continues and as the para-aortic nodes become increasingly large, varying degrees of discomfort or of actual pain manifest themselves. A noteworthy characteristic is a slow but more or less steady increase in discomfort or pain. In some cases this is interrupted at times by partial or complete relief for varying periods. At first the pain is often inconstant and slight, but as time goes on it gradually occurs more frequently until it becomes constant, and it also increases in severity. When the pain is constant, however, severe pain such as that which characterizes acute cholecystitis, nephrolithiasis or appendicitis is exceptional. In many cases the pain is described as a "dull ache" or "soreness."

Many patients complain of a heavy sensation in the epigastric region. Others complain of a sensation of "fulness in the stomach," especially after eating. Not infrequently a patient stresses his inability to eat a large or even an ordinary meal without discomfort, and some patients have learned that they can avoid distress by taking a small quantity of food at frequent intervals. Others voluntarily restrict themselves to milk and other liquid foods. This sense of undue fulness after eating appears to be a simple mechanical effect of the gradual increase in size of the para-aortic nodes or of both the para-aortic and mesenteric nodes and of the decreasing ability of the stomach to find room to expand with the amount of food taken.

Instead of a mere sense of heaviness or fulness, some patients complain of epigastric pain occurring from half an hour to three hours after meals and thus simulating the pain generally regarded as characterizing peptic ulcer. Gastroenterologists often speak or write of the pain of peptic ulcer as a "typical ulcer pain," but one cannot help

wondering if such an expression is warranted. Occasionally a patient with retroperitoneal lymphoblastoma may also have a gastric or duodenal ulcer, but another who does not have any ulcer may have the same kind of pain, and occasionally relief may follow the use of sodium bicarbonate just as is supposed to occur only in a patient with a gastric ulcer. Another point worth remembering is that in an occasional case a false roentgenologic appearance of duodenal ulcer may be produced by enlarged para-aortic lymph nodes in close anatomic relation to the pyloric end of the stomach, to the duodenum or to the head of the pancreas.

Occasionally pain in the epigastric region or in another part of the abdomen, such as the right lower quadrant, may become increasingly severe, and its character as well as the symptoms associated with it may suggest obstruction of some portion of the intestinal tract. In such a case an exploratory laparotomy may reveal obstruction of the duodenum, cecum or other part of the bowel by pressure from enlarged nodes adjacent to these structures or by actual infiltration of the intestine by the pathologic process affecting the nodes. Occasionally, also, pain in the epigastric region may be accompanied by nausea and vomiting, and roentgenologic examination of the stomach may disclose more or less extensive involvement of the organ. Careful exploration usually reveals more or less extensive involvement of the para-aortic or mesenteric nodes or both. Although it is possible for the intestine or stomach to be invaded independently by lymphoblastoma, it seems more likely that the intestinal or gastric involvement represents direct extension of the process from adjacent nodes. Lymphoblastoma sometimes has a distinct tendency to infiltrate adjacent tissues. This is seen when Hodgkin's disease or lymphosarcoma affecting the mediastinal nodes infiltrates the thoracic wall through the intercostal spaces and thus extends to the subcutaneous tissues or when it infiltrates the spinal canal.

In other cases the pain complained of is not in the epigastric region but is in the right iliac region or in the left side of the abdomen. Also, the pain may shift from one part of the abdomen to another, may vary greatly in duration and severity or may occur in waves strongly suggesting spastic contraction of the bowel, probably as a result of mechanical interference by enlarged para-aortic nodes or by enlarged nodes in the mesentery or both. Sometimes the pain is cramplike or colicky. When the pain is localized in the right iliac fossa or in the right upper quadrant of the abdomen it may be due to mechanical pressure on or infiltration of the right ureter by enlarged iliac nodes, sometimes causing partial or even complete obstruction of the ureter, with resulting hydronephrosis of the right kidney. The pain may also be due to

lymphoblastomatous infiltration of lymphoid tissue in the region of the appendix and cecum from adjacent right iliac nodes involved in the process; or it may be caused by pressure of enlarged iliac nodes against the ilium, and the pressure may be sufficient to cause erosion of the bone. When the pain is in the left lower quadrant it may be due to the first or third of the foregoing causes acting on that side.

Thus it may be seen that the character, site and severity of the pain may vary greatly, according to the nodes which happen to be the largest and the anatomic relation of the nodes to particular organs or structures.

Pain in the Back.—A rather common symptom of retroperitoneal lymphoblastoma is pain in the back. Some patients never have it, but many others suffer from it sooner or later, and in some cases it is the chief or only presenting symptom. Usually the pain is a dull ache and affects the lumbar region, but sometimes it extends to the lower part of the thoracic region or more often to the sacral region. In the beginning the pain is usually slight and may be described as a sort of "tired feeling" in the back. Inconstant at first, it gradually occurs more and more frequently and finally becomes practically constant; at the same time it increases in severity. Most patients describe it as a steady dull ache, which becomes severe or excruciating only when some of the spinal or pelvic bones become eroded by direct pressure or are invaded through the blood stream. In most cases it is worse at night than during the day. The pain may be entirely unilateral for some time but may later affect both sides. Even then it is usually more pronounced on one side, as a rule on the side on which it first developed; this is commonly the left side, although pain on the right side is almost as common.

Important features of this pain are its slow, gradual increase as the weeks and months roll by and its tendency to be projected to the corresponding hip and later down the corresponding lower extremity as far as the knee or the foot. Sometimes the patient also complains of numbness and tingling of the foot or of the foot and leg. Sometimes the pain around the knee and leg may be worse than the pain around the hip, or the latter may be absent altogether. When the backache affects both sides, just as it is usually more severe on the side affected, the pain in the corresponding hip and lower extremity is more severe than that on the opposite side.

This backache is undoubtedly caused by gradually increasing pressure of enlarging para-aortic lymph nodes on nerves which enter into the formation of the lumbosacral plexus. The circumstances all point to such a cause, and other reasons will be mentioned later.

Rarely, the pain in the back may appear with suddenness, and the circumstances may give an erroneous impression of traumatic origin. For example:

A woman of exceptional development and vigor, aged 36, who had always regarded herself as in the best of health, was driving her car. On coming to a stop and stepping out from the driver's seat, she was seized with a severe pain in the left side of the back. Instead of subsiding after a few days the pain had continued, increasing slowly but steadily week by week. Repeated examinations had failed to account for it. One and a half years after the day of onset she had been subjected to an unusually thorough examination, but a plausible cause for the pain had not been discovered. The possibility of enlarged retroperitoneal nodes had not been considered. As a palliative measure she had been fitted with a brace and instructed to return in three months. At the expiration of this interval she reported that the brace had provided considerable relief from the pain in the left side of the lumbar region but that the pain had "shifted" to the left hip, had been increasing steadily and now extended down the left lower extremity. She had considerable difficulty in walking. Ordinary and roentgenologic examinations again failed to furnish any clue to the cause of the patient's difficulty. Therefore, it was assumed that she must be suffering from sciatica, and she was referred for roentgen treatment.

The excellent general condition of the patient, the long duration of the pain and its gradual increase in extent and severity, the fact that the pain affected the lumbar region and was projected to the corresponding lower extremity and the fact that no other adequate cause could be found led me to suspect retroperitoneal lymphoblastoma. Physical signs of some kind of retroperitoneal adenopathy having been found,[4] roentgen treatment was planned on the assumption that if the pain was due to lymphoblastoma affecting the para-aortic lymph nodes it would be relieved largely or wholly within two to three weeks.

When the patient returned four weeks later the pain had almost disappeared. She was then given a second course of similar treatment and up to the time of this report has been entirely free from pain in the back or in the left lower extremity. Since then, however, lymph nodes in the neck and axilla have enlarged and have thus furnished clinical corroboration of the diagnosis of lymphoblastoma. In time other evidence of the process will doubtless appear.

This is the only case observed by me in which the backache seemed to develop suddenly. How can this seeming suddenness be accounted for? As the para-aortic nodes increase in size they adjust themselves to the surrounding tissues and to spaces between adjacent structures. When the available space is exhausted, however, the continued hyperplastic enlargement of the nodes begins to exert pressure on the bowel or stomach, on the nerves of the lumbosacral plexus or on other structures. In the case cited, anatomic adaptation had probably been taking place for a long time and had about reached its limit. In getting out of her car the patient had probably twisted herself in such a way as to crowd the enlarged retroperitoneal nodes beyond their limit of physiologic endurance, and pain had resulted.

4. These physical signs will be described later.

Occasionally a case is encountered in which the pain in the back, instead of being a dull ache, becomes severe or excruciating. This usually indicates erosion of spinal (lumbar) or pelvic bones by pressure of enlarging para-aortic or iliac nodes. Rarely, the pain in the lumbar region may remain dull while the pain radiating down one of the lower extremities gradually becomes so severe that the patient may be unable to tolerate even the weight of a sheet over the feet. Such excruciating pain indicates not mere pressure irritation on some branch or branches of the lumbosacral plexus but actual infiltration of the nerve or nerves. If this infiltration has not been present too long and if the affected nerves have not been injured beyond repair the pain can be relieved within one or two weeks by roentgen treatment. To direct the treatment to any part of the extremity itself is a waste of time, because the neural injury is usually not in the extremity but in the lumbar region. Treatment should be directed to the lumbar region and sometimes also to the lower part of the thoracic region in order to include all the nerve branches that go to form the plexus.

Because roentgenograms of the spine may disclose more or less pronounced evidence of chronic arthritis it is sometimes taken for granted that this condition is responsible for the backache; the patient may be given prolonged medicinal treatment or physical therapy, and tonsils, teeth, appendix or gallbladder may be sacrificed in a vain attempt to relieve the pain and remove its supposed causes. In spite of these measures, however, the pain continues with or without interruption. The slow but steady increase in pain, the presence of other symptoms pointing toward lymphoblastoma and especially the presence of lymphadenopathy in other regions should make one pause before assuming that the pain is due to arthritis. Occasionally, chronic arthritis in one or several parts of the body may be associated with lymphoblastoma. Hasty conclusions, therefore, are unwise. To assume that backache, with or without extension of the pain to the hips or lower extremities, is related to chronic alterations of the vertebral articulations revealed by roentgenography may result in injustice to the patient by robbing him of the chance of relief which in the case of lymphoblastoma might follow proper irradiation within a few days and sometimes within twenty-four hours. Chronic arthritis also may respond favorably to irradiation, but the response is much slower, and repeated treatment may be necessary to cause the pain to disappear.

In certain cases lymphoblastoma has a tendency to infiltrate tissues outside the lymph nodes, and this infiltration may become rather extensive. Thus, an entire breast or a breast and the superficial tissues of the corresponding half of the thorax may become densely infiltrated. Lymphoblastoma affecting the mediastinal nodes may infiltrate one or more intercostal spaces and may form a mass over the sternum; this

probably represents extension of the process along the lymphatic channels that accompany branches of the internal mammary vessels and may not be infiltration in the sense here referred to. Lymphoblastoma of the retroperitoneal nodes, however, may infiltrate the tissues of the back; this irregular and diffuse infiltration may extend to the spine and may even penetrate the spinal canal, involving the dura and cord and giving rise to various sensory and motor disturbances, which may be mistaken as indications of a primary tumor of the spinal cord.

Bloating and Belching.—Many patients include among their complaints a more or less pronounced tendency toward abdominal distention with gas, with or without a corresponding tendency to belch. Not infrequently, indeed, bloating, belching and a vague sense of epigastric discomfort may be the only symptoms noticed by the patient for several months and sometimes for several years. He may have consulted one or more physicians, who, not being aware that lymphoblastoma sometimes begins in the retroperitoneal nodes or disregarding the possible relationship of enlargement of nodes in other regions, may have treated the patient for achlorhydria, for peptic ulcer or for cholecystitis. Sometimes, because an obvious organic lesion is not found, the patient is branded as "neurasthenic," thenceforth to be shunned as a medical bore; or he is treated by "psychotherapy," or, more bluntly, by being given a "talking to" as if he were a malingerer.

When pronounced, distention and belching are greatest some time after eating, and they may be accompanied by soreness or actual pain. Some patients seek relief by taking sodium bicarbonate or by modifying their diet in various ways from the elimination of meats to the adoption of a diet exclusively of milk, but the degree of relief obtained varies greatly. Other patients mention bloating and belching after meals, without any pain or with only a sense of abdominal discomfort or of weight in the "stomach," by which the average person means the epigastric region or the abdomen in general.

These disturbances appear to result from some degree of mechanical interference by enlarged para-aortic or mesenteric nodes to the passage of gas from the loop of the duodenum into the jejunum; the main point of obstruction of gas, however, may be somewhat lower. Sometimes, with marked involvement of most of the para-aortic and iliac nodes, interference with the passage of gas may affect the colon as well as the small intestine, and abdominal distention, frequently accompanied by spastic pain, may be a prominent feature.

Nausea and Vomiting.—Less common than the aforementioned symptoms, nausea, alone or associated with vomiting, occurs often enough to deserve attention. At first slight, infrequent and irregular in their occurence, nausea and vomiting gradually tend to occur more

frequently; this, however, varies a great deal. Some patients have nausea without vomiting. In some cases nausea and vomiting never become a regular or prominent feature, whereas in others the time comes when, especially if the patient eats more than a small quantity of food, little can be retained, and weight is lost rapidly. The character of the food may be a definite factor; some patients report that they vomit only when they eat heavy or greasy foods. In certain extreme cases, however, nausea and vomiting may recur regularly after every meal, although some patients have learned by themselves that they can diminish the tendency by eating only liquid foods or by taking food in small quantities at short intervals. In most cases in which nausea and vomiting occur they are associated with a sense of weight, heaviness or pain in the epigastric region, with bloating and belching or with all these symptoms combined.

Fever.—At the outset, for a long time after it or throughout the course of their illness, most patients afflicted with Hodgkin's disease or lymphosarcoma do not have fever. It would be more accurate to say that they are not aware of fever. A certain proportion of patients do have fever, and it is probable that if the temperature of all patients should be taken regularly the proportion of febrile patients would be larger than it appears to be. Inasmuch as the fever in many cases is slight, many patients whose temperature rises above normal every day or almost every day are not aware of the rise until the fever is discovered by a physician. Often a patient's statement that he does not have any fever is accepted without verification.

Another point worthy of note is that if the distinction between Hodgkin's disease and lymphosarcoma which heretofore has been made and still is being made by pathologists is accepted, the fact remains that patients suffering from one condition or the other may have fever at some stage in the process, and the type of fever cannot be taken as an indication of the variety of lymphoblastoma. Patients with lymphosarcoma may have precisely the same kind of fever as patients with Hodgkin's disease.

Fever occurs almost always in the afternoon; the temperature in the morning is usually normal or subnormal. In some cases the fever is continuous, that is, it recurs daily for long periods, although it may be punctuated by occasional and irregular interruptions. As time goes on the fever gradually tends to increase, but this feature varies considerably in different cases. As the fever continues, the temperature in the afternoon tends to rise higher and higher; after a time the temperature in the morning also may be abnormal.

In other cases the fever occurs in waves, bouts or "attacks" which may last from one to several weeks, with a roughly similar interval

between them. During the first few days of each bout the afternoon fever is slight. Then the temperature increases slowly day by day to a maximum which in different patients may vary between 101 and 104 or 105 F. During the early stages of the malignant process the maximum temperature attained is rather low, but as the condition progresses the maximum during the successive bouts tends to rise. This is the type of fever to which the name "Pel-Ebstein" has been attached. When the malignant process is relatively acute,[5] the fever in successive bouts increases more rapidly than it does when the condition is chronic and continues for several years. As a rule, the Pel-Ebstein type of fever is more common in cases of relatively acute lymphoblastoma than when the lymphoblastomatous process is decidedly chronic, but exceptions are not rare.

An important point is that in either Hodgkin's disease or lymphosarcoma fever of the Pel-Ebstein or of the continuous variety indicates lymphoblastomatous invasion of the retroperitoneal or of the mediastinal nodes (usually the former). Moreover, this indication is so definite that it may be relied on even when enlarged abdominal nodes cannot be palpated. Why lymphoblastoma affecting the para-aortic or mesenteric nodes should cause fever and the same condition confined to the cervical nodes should not cause fever remains a puzzle. Nevertheless, the validity of this indication cannot be denied.

The reader will naturally ask on what grounds such a conclusion can be drawn. For years I have observed that when patients with Hodgkin's disease or lymphosarcoma have fever roentgen treatment directed exclusively to the abdomen through bilateral anterior and posterior fields causes the fever to abate or to disappear, whereas treatment directed to other regions but not to the abdomen causes the irradiated regional nodes to diminish in size but does not usually influence the fever. In a few cases, in which clear evidence of invasion of the mediastinal nodes was present but clinical evidence of invasion of the retroperitoneal nodes was uncertain, roentgen treatment directed to the mediastinum through bilateral anterior and posterior fields, with the four beams of rays converging on the mediastinal structures, was followed by reduction in the fever. However, the fields of irradiation were so large that they necessarily included some of the structures below the diaphragm, and this may have accounted for the lowering of temperature. It is for this reason that in the preceding paragraph the mediastinal nodes were included as a possibly associated, but doubtful, factor in this indication.

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5. It is never as acute as some of the infectious fevers. In the form here called "relatively acute" the course of the condition from onset to death may extend over a period varying between six months and two years. In the chronic form the process may continue from three to twenty-five years or longer.

Further circumstantial evidence of the relation between fever and lymphoblastomatous invasion of the retroperitoneal nodes is to be found in an occasional case in which the patient's chief symptom is fever, possibly associated with loss of strength and sometimes loss of weight. In such a case the physical signs [6] of enlarged retroperitoneal nodes can usually be found, although sometimes they are vague and indefinite. When all examinations of the blood, urine and sputum for malaria, Malta fever, infection with Brucella abortus, infection of the urinary tract, tuberculosis, actinomycosis or other possible causes of fever yield only negative information, irradiation of the abdomen in the manner previously specified may cause the fever to diminish or disappear within from one to three weeks and may thus point to retroperitoneal lymphadenopathy as the source of the febrile disturbance. This therapeutic test with roentgen rays should not be overlooked in a case of this kind, because it often gives invaluable help in the presence of otherwise unaccountable fever. If the dose of roentgen rays given to each field is small (less than 300 roentgens measured in air) or if roentgen treatment is given through a single anterior and one posterior field, its influence on the fever may be only slight and transient—sometimes too slight to be recognized as an effect of irradiation. Even with larger doses (400 to 600 roentgens) given through multiple fields, the antipyretic effect must not be expected to last indefinitely; it may last from two or three weeks to two or more months, but after a variable period of reduced fever or complete apyrexia the fever usually returns. If a second course of roentgen irradiation is given three or four weeks after completion of the first course the antipyretic effect is more pronounced and continues longer than after a single course.

An important exception must be noted: When the malignant process has reached an advanced stage or has entered the terminal phase, the antipyretic influence of roentgen irradiation directed to the retroperitoneal nodes is less pronounced, the fever may not abate, or any lowering of temperature which may follow may be short lived. Usually the prognostic significance of the effect of irradiation is supported by other indications: either limited, transient regression of the irradiated lymph nodes, failure of the nodes to regress, increasing adenopathy in other regions, continued loss of strength and weight, increasing anemia or vice versa.

Many authors who have written on roentgen or radium therapy for Hodgkin's disease or lymphosarcoma have reported observing after irradiation of the neck or the mediastinum an increase in fever which the patient already had or an onset of fever in a patient who was not known to have had it previously, and they have regarded this fever as a phase of the reaction to roentgen rays or to radium. I have never

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6. These signs will be described later.

had such an experience, although I have been watching for it for many years. The onset of fever or its increase in such a case almost certainly represents active invasion of the retroperitoneal nodes by the lymphoblastomatous process or increased activity of the same condition already established in these nodes. That extension of the process to the para-aortic or mesenteric nodes from some other group of nodes may follow irradiation of the latter is conceivable, but there is no good evidence to support the assumption that this is a direct effect of exposure to the rays. It seems much more likely that fever had been present previously but the patient himself had not been aware of it. or that the patient, having the Pel-Ebstein type of fever, did not have any fever immediately before the treatment but showed a rise in temperature during or soon after the irradiation; or that the systemic (gastrointestinal) reaction caused by irradition may indirectly have caused an increased activity in retroperitoneal nodes already affected by lymphoblastoma and may thus have been a factor in the onset of fever.

It must not be inferred that every unexplained fever is due to lymphoblastoma in the retroperitoneal nodes, but fever arising in a patient who is known to have Hodgkin's disease or lymphosarcoma points to invasion of the para-aortic or mesenteric nodes or both, whether enlarged nodes in the abdomen can or cannot be felt. In a patient with enlarged nodes in other regions suggesting the possibility of lymphoblastoma, the presence of fever, when it cannot be attributed to some infection, strengthens the possibility of lymphoblastoma and indicates the probable extension of the process to the retroperitoneal nodes. In a patient with lymphadenopathy in other regions, fever which cannot be traced to some infection may be due to lymphoblastoma affecting the retroperitoneal nodes and, if so, should abate or disappear for a time after irradiation unless the malignant process has reached an advanced stage.

Pruritus and Cutaneous Lesions.—Occurring in about the same proportion of cases as fever, pruritus may be the first or the only symptom noticed by the patient, or it may not develop until Hodgkin's disease or lymphosarcoma has been established for months or years. This does not imply that itching is to be expected only by a patient with fever; in fact, these two symptoms do not appear to be related, although in some cases they may both be present. As a rule the itching begins in one part of the body, such as the lower or upper extremities, and gradually extends to other parts. In some cases the face, the entire head or some other part of the body may be spared, while in others practically every inch of the body is affected. At first the pruritus is moderate, but gradually it becomes more and more severe until the patient spends much time and energy in scratching and finds it difficult

or impossible to sleep. Often the skin of the entire body is covered with scratch marks. Although the severity of the pruritus may vary considerably at different times, intense itching may continue for long periods.

Even when the patient is afflicted by intense pruritus, cutaneous lesions other than linear excoriations may be wholly absent. Sometimes, on the other hand, the itching is accompanied by macular, maculopapular or papular lesions which at first may be discrete and regional in their distribution but which, as they extend and increase, may gradually coalesce to form irregular patches. Exceptionally the skin may become diffusely infiltrated. This form also may have a regional or general distribution. Sometimes this infiltrative thickening of the skin is irregular; sometimes it is remarkably uniform. Still more rarely a case may be encountered in which the external appearance of the skin is entirely normal, the infiltration affecting only the deep layers of the skin and the subcutaneous tissues; this form of lesion is usually limited to one region, such as an upper extremity, but in time it may also affect the corresponding extremity on the opposite side without involving the skin or subcutaneous tissues of intervening regions.

When lesions of the skin are not present, those who are not familiar with the many vagaries of lymphoblastoma often fail to recognize the underlying cause of the pruritus because the relation between the two is not realized. When the pruritus is accompanied by circumscribed lesions or by a more or less general eruption, the condition is often mistaken for eczema, eczematoid dermatitis, scabies, psoriasis, urticaria, shingles or even impetigo.

Not every cutaneous eruption arising in a patient with Hodgkin's disease or lymphosarcoma is related to the malignant process. There is no reason why a patient afflicted with lymphoblastoma may not also have ordinary eczema, dermatitis or psoriasis, or why a patient with some form of dermatitis, scabies or psoriasis may not also become affected with lymphoblastoma. Hasty assumptions should by all means be avoided. Even when the cutaneous disturbance is definitely related to underlying lymphoblastoma it may respond to ordinary dermatologic treatment, but the degree of improvement is seldom great and the improvement is seldom lasting. When clear evidence of lymphoblastoma is provided by enlarged nodes which microscopically reveal the presence of Hodgkin's disease or lymphosarcoma or when numerous enlarged nodes in different regions suggest the probability of a lymphoid disorder of this kind, the association of local or general pruritus, with or without lesions in the skin, should always make one think of lymphoblastoma as a possible cause.

Just as, for reasons still unknown, fever is related to and is a sign of lymphoblastomatous invasion of the retroperitoneal nodes, so also pruritus and the cutaneous lesions with which it may be associated constitute another sign that the malignant process has extended to the para-aortic nodes or to these and to the mesenteric nodes as well. The same observation which has been mentioned in connection with fever applies also to pruritus. Roentgen irradiation directed to regions of the body other than the abdomen,[7] with the possible exception of the mediastinal nodes, does not influence the itching or the cutaneous lesions; but irradiation directed to the abdomen through large bilateral fields on both the anterior and posterior aspects causes the itching and the lesions to diminish or disappear. Moreover, the rate at which these manifestations subside or vanish corresponds to the rate at which lymph nodes affected by lymphoblastoma are known to be influenced by roentgen rays. As has been indicated, it is possible that lymphoblastoma in the mediastinal nodes also may play a part in the toxic cutaneous manifestations. Sometimes irradiation directed to the mediastinum may be followed by improvement in the condition of the skin, but even when the enlarged nodes decrease greatly in size the improvement which may follow mediastinal irradiation is slight as compared with the influence of roentgen rays on the retroperitoneal nodes. Inasmuch as when the mediastinal structures are irradiated the fields exposed usually are large enough to include some of the structures in the upper part of the abdomen, it is possible that the effect on the pruritus and on the cutaneous lesions may result from the action of the rays on retroperitoneal nodes included in the fields of irradiation rather than on the nodes in the mediastinum.

Increased Pigmentation of the Skin.—In a small percentage of cases the color of the skin becomes darker than normal. This change may be slight and the skin may have a muddy or dusky appearance, or the increase in pigment may gradually become so great that the skin becomes light dirty bronze. In the axilla and groin the skin is still darker. Sometimes the pigmentation suggests Addison's disease, but the other stigmas usually are absent. Whether this abnormal increase in pigment is due to lymphoblastomatous invasion of the adrenal glands or of aberrant chromaffin tissue is not yet clear. At any rate, it is certainly caused by a disturbance in the formation or distribution of pigment. Whatever may be the mechanism involved in this change, increased pigmentation of the skin is another indication that the lymphoblastoma has invaded the retroperitoneal lymph nodes. Unless the malignant process has reached an advanced stage, well planned roentgen irradiation can be counted on to improve the patient's condition. As the affected lymph

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7. When the entire abdomen is shielded from exposure.

nodes in different parts of the body diminish in size, the pigmentation gradually decreases. After several courses of treatment the skin may have resumed an almost normal color, but in most cases this ideal result is never achieved, and some degree of abnormal pigmentation persists indefinitely.

Constipation.—Many patients with Hodgkin's disease or lymphosarcoma complain of constipation, the degree of which is often proportional to the degree of other symptoms, such as bloating and belching, pain in the abdomen or in the lumbar portion of the back, fever and itching. Constipation is so prevalent in otherwise normal persons that too much significance must not be attached to it. Nevertheless, the onset of constipation in a person who has never or seldom been troubled with it and its steady increase, sometimes to such a point that daily enemas become insufficient to clear the colon, should lead one to relate it to enlargement of the para-aortic or mesenteric nodes and to consequent mechanical interference with the motor function of the bowel, especially when other concurrent indications of retroperitoneal adenopathy are present. Absolute proof of such a relation cannot be submitted, but strong circumstantial evidence is available. Often the constipation diminishes or disappears after roentgen irradiation of the abdomen has caused the enlarged retroperitoneal nodes to retrogress. Later, as these nodes enlarge again, the constipation returns. A succession of similar cycles can sometimes be observed.

Diarrhea.—Diarrhea is not a common symptom but does occur in certain cases. Sometimes it takes the form of short bouts, the duration of which may vary from two or three days to one or two weeks, the bouts recurring at varying intervals. Occasionally the diarrhea may continue indefinitely, although it may vary considerably in degree from time to time. Generally slight at the beginning, it tends to increase gradually. The patient loses weight and strength, sometimes at an alarming rate. Often there is a ravenous appetite, and the quantity of food eaten may be greater than normal. Nevertheless, weight and strength continue to decrease slowly or rapidly according to the severity of the diarrhea. The patient may lose from 10 to 40 pounds (4.5 to 18 Kg.) in from one to six months, and ordinary efforts at treatment may be of little or no avail; any improvement obtained usually proves only temporary. Suitable exposure of the abdomen to roentgen rays, on the contrary, is often followed by striking improvement. Unfortunately, the favorable effect of a single course of treatment is only temporary; the duration of this effect varies considerably in different patients. Repeated irradiation of the abdomen may arrest the diarrhea permanently, but the evolution of the malignant process may not be otherwise influenced. In all probability, diarrhea with or without

tarry stools indicates infiltration of the bowel (solitary follicles and Peyer's patches) by the lymphoblastomatous process.

Edema.—Although relatively uncommon, edema occurs often enough to deserve attention. If lymphoblastoma is considered as a whole and not only as it affects the retroperitoneal, iliac and pelvic nodes, edema of the lower extremities occurs somewhat more frequently than edema of the upper extremities, but the difference is not great. In the lower extremities it usually affects first the feet and ankles and may then gradually extend to the legs; only in exceptional cases is the edema sufficiently pronounced to affect an entire lower extremity, and it is still more rare for the edema to affect the scrotum and the lower part of the abdominal wall. Bilateral edema usually is greater on one side than on the other, and nearly always this is the side on which the edema first appeared.

When a cardiac or renal disturbance cannot be found to explain it, edema of one or both lower extremities or of some portion of them indicates not blockage of the femoral vessels by enlarged inguinal nodes but interference with circulation through the external iliac vessels by enlarged external iliac nodes. When edema has extended also to the lower part of the trunk, notably to the scrotum, penis, pubic region and lower portion of the abdomen, it indicates interference with circulation through the common iliac vessels by enlarged common iliac nodes. The degree and extent of the edema may vary according to the degree of interference by the nodes; as a rule this is roughly proportional to their size, but not always. The anatomic relation of the nodes to the vessels appears to be as important as their size. Interference with circulation below the bifurcation of the common iliac vessels is generally compensated by increased circulation through collateral vessels. In cases of edema of the lower extremities, deep palpation in the iliac regions on one or both sides usually reveals enlarged nodes, which may be distinctly felt as such, or an abnormal diffuse resistance without perceptible nodulation. In either case pressure on the nodes or on the resistance elicits slight or moderate tenderness. Of course, when the abdominal wall is thick with fat or exceptionally muscular or when the abdomen is distended with gas or fluid, these physical signs may be difficult or impossible to make out. Exposure to roentgen rays causes the edema to diminish or disappear more or less rapidly as the nodes retrogress. The only exceptions are seen in cases in which the malignant process has reached an advanced stage or in which frequently repeated exposures to excessive quantitative doses of rays have caused the nodes to become resistant to irradiation.

Ascites.—In some cases of Hodgkin's disease or lymphosarcoma affecting the abdominal nodes ascites may be present when the patient

first consults a physician. This does not mean that fluid in the peritoneal cavity is an early sign of lymphoblastomatous invasion of the abdominal nodes. Almost invariably a careful inquiry into antecedent events reveals that the patient has had various gastrointestinal or abdominal disturbances for weeks, months or years. These disturbances may have been vague or definite, and the patient may have sought medical advice previously, but the cause of the symptoms often has not been recognized or even suspected. The ascitic fluid may be clear serum, a mixture of serum and blood or chyle. When the fluid is serous, the ascites is due to interference with the portal circulation. When the fluid is serosanguineous, the previous factor is associated either with erosion and hemorrhagic extravasation along the intestinal tract or with modifications in the blood, causing it to seep through the vessels and tissues at points where these have been weakened by the pathologic process. When the fluid has the character of chyle, the portal vessels are *not affected*; the seepage of chyle is due to blockage of the mouth or the lower part of the thoracic duct by enlarged para-aortic nodes.

When lymphoblastoma involves the abdominal nodes primarily or secondarily it may be confined to the para-aortic nodes or to the para-aortic and mesenteric nodes for a long time, but sooner or later, the malignant process may extend to other groups of nodes; in extreme cases all the lymph nodes and other aggregations of lymphoid tissue, such as the intestinal follicles, Peyer's patches and the lymphoid tissue in the appendix and in the vicinity of the ileocecal valve, may become infiltrated. Sometimes the para-aortic, mesenteric and other nodes become so large or are so situated with reference to the portal vessels that they impede the circulation through these vessels. Sometimes the para-aortic nodes in the vicinity of the celiac axis become so large that they block the receptaculum chyli sufficiently to cause chyle to seep into the peritoneal cavity. In other cases the close anatomic relations between these nodes and the stomach or duodenum may lead to lymphoblastomatous infiltration of these structures, and seepage of blood or frank hemorrhage may result.

Jaundice.—When first examined many patients appear pale, and some have a pasty or sallow complexion. Not infrequently the skin and the ocular conjunctiva have a faintly yellowish tint, but this is seldom sufficient to be designated as jaundice. True jaundice of any degree is comparatively rare. That it can occur, however, is undeniable, and its presence indicates one of three possible causes: when slight it indicates (1) impedence of the flow of bile through the common bile duct from infiltration of the duct by enlarged lymph nodes or (2) changes in the blood, or both; when marked, it indicates (3) lymphoblastomatous infiltration of the liver. The last usually represents an advanced stage of the disease.

When anemia or involvement of the liver is not present, the pale, pasty or sallow appearance of the skin often gives way to a more healthy appearance when roentgen therapy causes the lymphadenopathy to retrogress and the patient's general condition to improve. This improved appearance may last only a short time, or it may continue for months or years, especially in the chronic form of the disease. True jaundice, on the contrary, is seldom influenced favorably for a long time, if at all, probably because its presence denotes advanced lymphoblastoma.

Urinary Disturbances.—Occasionally a patient may include among his symptoms an increased frequency of urination and sometimes hematuria. Under these circumstances the possibility of hydronephrosis or pyelonephrosis must be kept in mind. The condition may be due to pressure on the ureter by enlarged iliac or para-aortic nodes or to infiltration of the ureter or of the renal pelvis by direct extension of lymphoblastoma from adjacent para-aortic nodes. Rarely, the kidney itself may be affected by the same process or through the blood stream.

Symptoms Related to Pelvic Organs.—Besides the many symptoms resulting from lymphoblastomatous invasion of the para-aortic, mesenteric and iliac nodes, some patients complain of increasing frequency of urination. In males this may be due to coincident hypertrophy of the prostate gland or to prostatitis, and in females it may be related to an associated fibromyomatous condition of the uterus. Frequently, however, conditions such as those mentioned cannot be found. Some patients complain of a dull soreness in the pelvis, some mention the passage of increasing quantities of mucus with the feces, but the majority of patients do not have any symptoms to suggest pelvic involvement. In a few cases one of the patient's symptoms, and sometimes the chief or only complaint, is irregular menstruation or complete amenorrhea. Pelvic disturbances may be a direct result of lymphoblastomatous invasion of pelvic lymph nodes or an indirect result of invasion of the para-aortic nodes; sometimes they may be the patient's first indication that all is not well, but usually they develop later in the course of the disease. As a rule they are associated with other symptoms, such as lymphadenopathy, loss of weight, lumbar backache, fever or pruritus. Amenorrhea as one of the chief symptoms is uncommon and usually occurs in young women. Amenorrhea or irregular menstruation arising after other manifestations of lymphoblastoma have been present for some time is much more common.

By itself, not one of the symptoms described can be taken as pathognomonic of abdominal lymphoblastoma, but when the history points to a gradual increase in any of them, with or without variations or remissions, the possibility of lymphoblastoma affecting the retroperitoneal

nodes should be considered. When enlarged nodes in other regions are present and when one or several of the symptoms mentioned develop and progress more or less steadily, the possibility of abdominal lymphoblastoma becomes a probability. When the patient is known to have Hodgkin's disease or lymphosarcoma, the appearance of one or more of the symptoms described increases the probability of invasion of the retroperitoneal nodes to a greater or less extent, according to the definiteness and degree of the symptoms.

Physical Signs.—Slight primary or secondary involvement of the para-aortic lymph nodes by Hodgkin's disease or lymphosarcoma probably does not produce physical signs that can be recognized by the methods of examination now available; also it probably does not cause any symptoms. But when the process has evolved and the size of the nodes has increased sufficiently to cause functional disturbances, certain physical signs usually are present; they may be so slight as to be difficult to perceive, or they may be so marked that it is hard to understand how any one could fail to recognize them. That they often go unrecognized or that they are often mistaken for something else is a matter of frequent observation. One reason is that the frequency of abdominal lymphoblastoma is not realized, and another reason is that few physicians have learned how to examine the abdomen for malignant invasion of the retroperitoneal nodes.

To examine the abdomen of a patient for metastasis to the retroperitoneal lymph nodes with some chance of obtaining maximum information, certain conditions must be fulfilled. The patient must be placed in a recumbent position with the head slightly flexed on the thorax. Still more important, the thighs should be flexed on the trunk and the upper extremities should be at rest along the trunk. The patient's breathing through the mouth may help to relax the anterior abdominal wall.

When the abdomen of a normal person is examined, unless the anterior abdominal wall is obese or exceptionally muscular or unless the abdomen is distended with fluid or gas, downward pressure yields a sensation of hollow organs containing air or gas, and the wall can be depressed until it comes in contact with the spine without any other adventitious resistance being encountered. Moreover, the only sensation experienced by the patient is that of the pressure exerted by the examiner's hand. Although this pressure may be more or less uncomfortable, there is no tenderness. When their attention is drawn to it, most patients can readily distinguish between actual tenderness and the discomfort caused by mere pressure, even when tenderness is slight.

When the para-aortic nodes are affected by lymphoblastoma and have attained a large size (fig. 4), they are sometimes readily felt as nodular masses in the epigastric or in the right or left hypochondriac region

Sometimes palpable masses are scattered throughout the abdomen. In most cases of this kind the mass or masses are fixed and do not move with respiration, but in some they have a limited degree of mobility. Occasionally a case is encountered in which one or more tumors may be moved readily, as if connected by a pedicle. This is likely to mean that the movable node or nodes are related to the mesocolon or are situated in the peripheral portion of the mesentery of the small intestine. Certainly it would be difficult to understand how any of the para-aortic

Fig. 4.—Mass of enlarged para-aortic nodes in a case of lymphoblastoma. As may be seen, the mass extends from the celiac axis to slightly below the bifurcation of the abdominal aorta. In some cases the nodes are much larger than those shown.

nodes or of the nodes in the root of the mesentery could have more than a slight degree of mobility.

In lymphoblastoma the spleen or liver or both may be enlarged independently of the retroperitoneal nodes or as part of the pathologic process affecting these nodes. When the spleen is invaded it may enlarge slightly or moderately, but almost never does it assume the proportions

encountered in myeloid leukemia. When metastasis to the liver occurs, this organ also may enlarge slightly or moderately, but as a rule hepatic metastasis is a relatively late complication. To many physicians a mass in the left upper quadrant of the abdomen must represent the spleen or the left kidney, and a mass in the right upper quadrant must represent the liver or the right kidney. Usually there is little difficulty in distinguishing the spleen or the liver from enlarged retroperitoneal nodes provided the possible involvement of these nodes is kept in mind and the examination is arranged accordingly.

Another point not infrequently leads to misinterpretation: When the lower border of the liver can be felt below the costal margin, it is often assumed that the organ is abnormally large. The mere fact that the lower border of the liver extends below the costal margin does not constitute proof of enlargement; it proves only that the lower border of the organ is lower than normal. When retroperitoneal lymphoblastoma is followed closely and systematically, it is found that as the para-aortic nodes (and the mesenteric nodes also when they are involved) retrogress after roentgen irradiation the liver frequently returns to its normal position. Therefore, it seems most likely that at the time of the first examination the liver was not abnormally large but had gradually been crowded forward and downward as the size of the retroperitoneal nodes increased. The position of the para-aortic nodes on each side of the abdominal aorta, as well as in front of it and behind it, and the important group of these nodes in the region of the celiac axis (behind the stomach and in close relation to the pancreas) often brings them in close relation with the crura of the diaphragm. When the lympho-blastomatous process affects not only the para-aortic nodes but the mediastinal nodes also, and when all these nodes attain the considerable volume they sometimes do, all the structures situated in front of the nodes are gradually crowded more and more toward the front. This undoubtedly explains the abdominal discomfort, soreness or pain, the sense of heaviness or fulness in the epigastric region after eating, the inability of many patients to eat a full meal and also the forward and downward displacement of the liver. Even when the mediastinal nodes are not perceptibly affected, the involved para-aortic nodes may be so large as to displace the liver. To some extent the spleen also may be displaced downward by the enlarged para-aortic nodes.

In the majority of cases of lymphoblastoma affecting the retro-peritoneal nodes primarily or secondarily, definite masses cannot be felt. This is why the average physician so often fails to recognize the physical signs of such involvement. Unless he can feel a mass or masses the size of a golf ball or baseball he concludes that a tumor is not present. In most cases of abdominal lymphoblastoma, masses of any size cannot

be palpated, probably because the para-aortic and mesenteric nodes are not large enough, because they are closely packed or because they are covered by other structures (intestine, omentum) to such an extent that individual nodes cannot be perceived. When pressure on the anterior abdominal wall is made, the examiner's hand feels in the upper half or the upper two thirds of the abdomen a deep resistance which is abnormal. This may be slight or marked; it may be more pronounced on one side than on the other, or it may be evenly distributed across the epigastric region and may extend into the right and left hypochondriac regions as well. When this deep resistance is greater on one side than on the other or when it appears to be confined to one side, it often extends longitudinally into the lumbar and sometimes also into the iliac region on the same side. In a large proportion of cases a considerable difference between the two sides is unmistakable. Many physicians recognize this resistance without realizing its significance; some ascribe it to muscular rigidity. And yet in most cases there is a clear difference between ordinary muscular rigidity and the deep resistance caused by enlarged retroperitoneal nodes. The former is immediately beneath the hand and is resilient or yielding, although this characteristic may be slight. The abnormal resistance due to malignant involvement of the retroperitoneal nodes is deeper and is not resilient. It may yield to pressure, but always one has the sensation of something solid. This sensation of solidity may vary considerably; sometimes the consistency is firm, and sometimes it is rather soft and boggy. In some cases a sense of vague nodulation can be perceived, while in others the deep resistance is diffuse.

When the deep resistance is marked and especially when it is diffuse and has a boggy or doughy character, lymphoblastomatous involvement of the mesenteric nodes also may be suspected. Inasmuch as the consistency of the enlarged nodes depends partly on the relative acuteness or chronicity of the malignant process and partly on its stage of evolution in the different patients, considerable variation is to be expected. Relatively speaking, the more acute the lymphoblastoma and the more rapid its evolution, the softer and the more boggy the lymph nodes tend to be. At necropsy in cases in which the deep resistance in the epigastric and umbilical regions was notably diffuse and boggy the mesentery has been observed to be so thoroughly infiltrated with closely packed hyperplastic lymph nodes that its thickness varied (fig. 5) between ½ inch and nearly 1 inch (1.3 and 2.5 cm.). Sometimes deep resistance in the epigastric or umbilical region may be so slight as to leave one in doubt. Deep palpation should then be made on each side of the spine and outward in the hypochondriac, lumbar and iliac regions.

The other important sign is tenderness. When a sensation of deep abnormal resistance is obtained, pressure on the resistant tissues or structures elicits a slight or moderate tenderness which is not normal.

The patient says, "That hurts," and winces or tries to draw away. The tenderness is seldom severe, but it is usually definite enough to leave no doubt. Until their attention has been drawn to it, some patients are inclined to attribute this tenderness to the pressure made by the examiner; but when their attention is directly attracted and pressure is made on another region for comparison, few patients have any difficulty in recognizing the difference. Even when deep resistance cannot be clearly perceived, slight or moderate tenderness on deep palpation should be regarded as abnormal. If the history suggests lymphoblastoma or if other clinical features of the condition are present, tenderness on deep palpation of the abdomen changes the possibility of invasion of the retroperitoneal nodes into a probability.
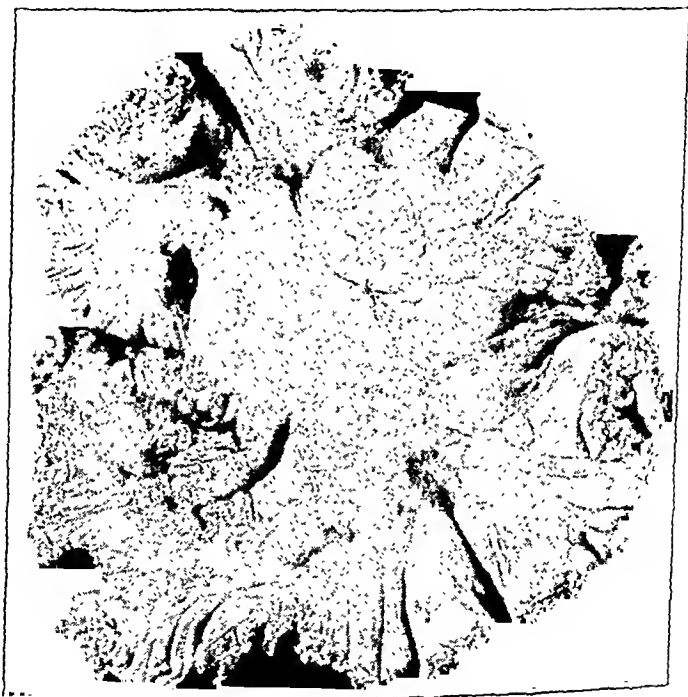
Fig. 5.—Massive infiltration of the mesenteric lymph nodes in a case of lymphoblastoma with extensive invasion of the abdominal lymph nodes. The hyperplastic nodes in the mesentery were so closely packed that the entire structure was diffusely and greatly thickened.

Physical Signs Related to Pelvic Disturbances.—In the majority of cases, when a patient afflicted with Hodgkin's disease or lymphosarcoma is subjected to rectal or vaginal examination, evidence of enlarged pelvic lymph nodes cannot be found. In a minority of cases moderately enlarged nodes may be found on the pelvic floor, and sometimes large masses in the pelvis may be discovered. When the patient is a woman, it is important to distinguish such a mass from a fibroid uterus, from an ovarian cyst or from pyosalpinx. As a rule, the history of the patient

illness and other physical signs help to make this distinction, but one must remember that two or all three of these conditions may be coincidental in the same patient. When amenorrhea or irregular menstruation is present, evidence of pelvic adenopathy may be entirely lacking; these symptoms may be due to deterioration in the patient's general condition, usually resulting from involvement of the retroperitoneal nodes.

Occasionally, proctoscopic examination of the rectal and sigmoid portions of the colon may disclose extrinsic lesions, but even intrinsic lesions may be found, and these may be mistaken for carcinoma.

Uncommon or Rare Findings.—Auscultation along the median line of the abdomen may sometimes elicit an abnormal bruit the nature and cause of which may be puzzling. As the retroperitoneal nodes regress after roentgen irradiation of the abdomen this bruit diminishes or disappears, but it may return some weeks or months later. Blackford [8] reported such a case in 1928. The rate at which this bruit diminishes or disappears after roentgen irradiation corresponds to the rate at which the lymphoblastomatous retroperitoneal nodes are caused to retrogress by irradiation. It seems probable, therefore, that the abnormal bruit is due to crowding or interference with the normal expansion of the abdominal aorta by a ring of enlarged retroperitoneal nodes, which may even cause partial constriction of this vessel.

Roentgenologic Findings.—In a great majority of cases in which the para-aortic lymph nodes are affected by Hodgkin's disease or lymphosarcoma, roentgenologic examination of the gastrointestinal tract does not yield any evidence of abnormality. Sometimes, however, local abnormality of contour, otherwise known as a "filling defect," may be found in the stomach or in the small or large intestine. Usually the defect is not constant in outline and is caused by extrinsic pressure. Occasionally the defect in the outline of the gastric or intestinal lumen is permanent (intrinsic) and may lead the most practiced roentgenologist into regarding it as evidence of carcinoma. Even the surgeon who undertakes to operate in such a case may be deceived, and the real character of the lesion may not be realized until the pathologist has examined sections of excised tissue. When the stomach is involved, the natural question is whether or not the diseased part of the organ should be resected. Inasmuch as in most cases gastric involvement is probably secondary to antecedent disease affecting the upper para-aortic nodes immediately behind the stomach, it would seem wise, before undertaking to excise a part of the organ, carefully to explore the entire region for enlarged nodes, especially the tissues along the upper part of the abdom-

8. Blackford, L. M.: Tumor Compressing the Abdominal Aorta, Proc. Staff Meet., Mayo Clin. **3**:191-193 (June 27) 1928.

inal aorta. If the para-aortic nodes are involved, the advisability of gastric resection would seem at least doubtful.

Sometimes a permanent "filling defect" may be found in the cecum. This portion of the colon may be obstructed more or less by lymphoblastomatous infiltration, and intussusception may have occurred. An enterostomy may have to be performed to relieve the immediate difficulty, but the advisability of resecting a portion of the colon and perhaps also a portion of the small intestine would seem to depend on the presence or absence of lymphoblastoma in the para-aortic, mesenteric or common iliac nodes.

In some cases roentgenographic examination of the spine may reveal more or less pronounced arthritic changes; these changes may or may not be connected with the pain in the back, hips or lower extremities, and such a relation should never be assumed without careful consideration of all factors. Lymphoblastoma and chronic arthritis may each play a part, or the pain may be due to one or the other condition.

When a patient complains of increasingly severe backache, roentgenologic examination of the spinal and pelvic bones may occasionally disclose more or less extensive destruction of one or more of the lower dorsal or lumbar vertebrae or of a portion of the iliac bones. The question is whether such destruction has resulted from pressure and secondary infiltration by enlarging para-aortic or iliac nodes or whether disintegration of the affected bone or bones is secondary to involvement of the bone marrow. An absolute answer to this question cannot be given at present, but in many cases the presence of contiguous nodes which have been enlarging gradually for some time seems to indicate that pressure erosion is probably a more common factor than extension outward from intrinsic involvement of the bone marrow. Another point in favor of this view is that as the retroperitoneal or iliac nodes retrogress after roentgen irradiation, some degree of repair of the affected bones is frequently observed. This bit of circumstantial evidence, however, is not conclusive, because when the para-aortic or iliac nodes are irradiated the affected vertebral or iliac bones also are exposed to the rays. Unfortunately, such involvement of bone usually accompanies extensive and rather advanced disease.

Occasionally urographic examination may disclose dilatation of the ureter and of the pelvis of the corresponding kidney, but an experienced urologist seldom has any difficulty in recognizing the fact that these abnormal appearances are due to extrinsic pressure. Rarely, however, the pelvis of the kidney and sometimes the kidney itself may be infiltrated by lymphoblastoma. In such a case, symptoms, such as hematuria, and other clinical features usually point to the disturbance. Even when enlarged lymph nodes in other regions cannot be found, a radiotherapeutic test may be required to solve the problem.

ACUTE SEGMENTAL APPENDICITIS

EXPERIMENTAL AND CLINICAL STUDIES

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In a previous communication [1] attention was called to a segmental type of appendicitis, characterized by a sharply demarcated lesion involving only a part of the organ. Further observations have revealed that not only does the single area of segmental involvement occur, but occasionally "skip" appendicitis, in which two or more areas of focal inflammation are separated by apparently normal appendical tissue. The gross features were particularly striking since they bore a close similarity to lesions seen elsewhere in the intestine.[2] The present study is concerned with the genesis of acute segmental appendicitis.

ANATOMIC CONSIDERATIONS

The experimental production of acute segmental appendicitis in the rabbit rests on two basic factors. The first is the peculiar segmental distribution of the appendical blood supply. The second is the striking similarity of the pathologic picture observed after vascular ligation in the rabbit to the pathologic process observed in man.

Certain embryologic and anatomic considerations are of interest in connection with the appendix and its blood supply. The organ may be regarded as a part of the general cecal pouch which has persisted in its early stage of development. Huntington [3] stated that "all the varieties of cecal apparatus met with in different species can be traced to one common primitive type from which they have all developed in accordance with varying conditions of alimentation." In herbivora, such as the rabbit and the horse, "whose food contains a relatively small amount

1. Felsen, J.: The Pathological Appendix, Am. J. Roentgenol. **31**:340 (March) 1934.

2. Felsen, J.: Cases of Intestinal Ulceration with Special Reference to Amebic Dysentery, Am. J. Digest. Dis. & Nutrition **1**:297 (July) 1934.

3. Huntington, G. S.: The Cecum and Vermiform Appendix, Soc. Lying-In Hosp. Med. Rep., 1893-1894; cited by Kelly and Hurdon.[4]

of nutriment in proportion to bulk and requires a longer time to digest we find a most complicated and highly developed cecal apparatus." The appendix is proportionately larger than the human appendix. In carnivora, such as the cat family, "whose food is concentrated, easily and rapidly digested and contains little nonnutritive material, the cecum is reduced." The appendix is relatively smaller than that of man. Because of these factors the rabbit's appendix closely approximates in size that of man. We shall now attempt to point out the similarity in blood supply, for it is these two features which make the rabbit peculiarly suitable for the experimental work to be described.

In the 7 month human fetus the blood supply of the cecum and that of the appendix are separate except for some minor anastomoses at the junction of these organs. Kelly and Hurdon [4] stated that in man there is usually a single appendical artery which arises directly from the posterior ileocecal artery or from one of its branches and is carried in the free edge of the mesentery. This vessel supplies the entire appendix and sometimes a small part of the adjacent cecum in about one third of the cases. In the remainder it supplies only the distal four fifths of the appendix, accessory arteries supplying the proximal portion and anastomosing with cecal branches. From the main appendical vessel arise generally five secondary branches, which proceed direct to the appendix. Although Romanis and Mitchiner,[5] in common with other authors, have stated that the tip of the appendix often receives a poor blood supply because the mesentery stops somewhat short of it, Kelly and Hurdon observed no such deficiency. Each of the five secondary branches described divides near the mesenteric border of the appendix into two or more subdivisions. After penetrating the wall of the appendix these vessels form two main intramural networks, the serosal and the submucosal. The former sends some branches to the muscular coats. The latter penetrates the muscularis to reach the submucosa, whence most of the branches pass to the mucosa. There they form delicate filamentous networks which embrace the solitary acuminate lymph nodules and send branches into their substance. Other branches reach the crypts and the mucosa. We have been able to demonstrate the distribution of these vessels by means of transparencies, with and without previous injection.[6] It appears that the extreme paucity of anasto-

. 4. Kelly, H. A., and Hurdon, E.: The Vermiform Appendix and Its Diseases, Philadelphia, W. B. Saunders Company, 1905.

5. Romanis, W. H. C., and Mitchiner, P. H.: The Science and Practice of Surgery, ed. 6, London, J. & A. Churchill, Ltd., 1937, vol. 2.

6. Felsen, J.: Intestinal Illuminator: A Device for Detecting Intestinal Lesions in Postmortem Specimens by Reflected and Transmitted Light, J. Lab. Clin. Med. 21:923 (June) 1936.

motic branches within both the mesentery and the appendical wall justifies the practical consideration of the five branches of the main artery as terminal vessels. Previously described by Van Cott,[7] Brunn[8] and others, the subject was admirably presented in 1927 by Graham[9] and in 1932 by Seng.[10] By injecting an opaque substance into the vascular system of the appendix in human cadavers, the latter demonstrated that the submucosal and serosal vessels are connected only by capillaries and thus are really terminal arteries. Brunn went so far as to divide the appendix into from seven to fifteen segments, each with a restricted vascular supply, and described sharply segmental inflammatory lesions.

Before proceeding to a consideration of experimental and clinical segmental appendicitis it seems fitting to recall the classification of the main appendical arterial supply by Kelly and Hurdon, since anomalous vessels must be considered in evaluating our experimental and clinical data. These authors recognized four types of main appendical arteries:

1. A single vessel supplying the entire appendix but no portion of the cecum. It usually arises from the ileocolic artery. This type of blood supply is present in one third of the cases.

2. More than one vessel, the first arising as in type 1 and supplying the distal four fifths of the appendix. The proximal portion of the appendix is supplied by one or two branches of the posterior ileocecal artery. This type is present in one quarter of the cases.

3. One or more vessels supplying both the appendix and the adjacent cecum, arising from the posterior ileocecal artery. Ligation of the proximal appendical artery may result in necrosis of the cecum. This type occurs in one quarter of the cases.

4. Loop formation between the main arteries as in the mesentery. This type of blood supply is of rare occurrence.

The general anatomy, including the vascular supply, of the cecal appendage (hereafter referred to as the appendix) in the rabbit (Lepus cuniculus) is comparable to that of the human appendix. There are, however, approximately twelve secondary branches, and the main appendical vessel lies close to the edge of the organ. These branches communicate with a vessel which lies in the mesentery of the adjacent

7. Van Cott, in Fowler, G. R.: A Treatise on Appendicitis, Philadelphia, J. B. Lippincott Company, 1894.

8. Brunn, W.: Ueber das Segmentäre bei der Wurmfortsatzentzündung, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **21**:1, 1909.

9. Graham, G. S.: The Vascular Factor in Appendicitis, South. M. J. **20**:365 (May) 1927.

10. Seng, H., in Aschoff, L.: Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., Ltd., 1931.

ileum and runs parallel to it. The interior of the cecal pouch possesses a complete spiral valve, and the mucosa of the appendix is richly supplied with solitary acuminate lymph nodules.[11] The intramural branchings are similar to those seen in man, and there are no appreciable anastomoses between adjacent branches. They are, therefore, essentially terminal vessels.

EXPERIMENTAL METHOD

In our studies, as has been stated, rabbits were used. The general method of procedure was to anesthetize the animal by intravenous injection of pentobarbital sodium, 1 grain (0.06 Gm.) for each 5 pounds (2.3 Kg.) of body weight, after which the abdomen was prepared and the appendix exteriorized under the usual conditions of surgical asepsis. After ligation of the vessels with catgut, observations were generally made for a limited period on the exposed appendix, the organ being suitably protected by warm gauze pads. The appendix was then returned to the abdomen, and the laparotomy wound was closed and dressed. Subsequent studies were made at varying intervals, after which the animal was killed. In referring to the technical procedures a schematic drawing (fig. 1) will be used as a key, the numbers indicating the secondary branches, starting with
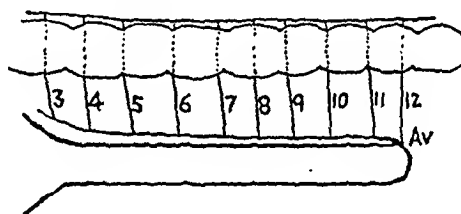
Fig. 1.—Vascular supply of the rabbit appendix. (Branches from AV to the appendix not shown.)

the base of the appendix. *A* and *V* refer to the main appendical artery and vein, respectively. Owing to the close proximity of the main artery and vein it was often difficult to ligate them separately without undue trauma. *In the case of* the secondary branches both vessels were always occluded together. It was deemed advisable to refer to the secondary vessels, starting with the distal, or no. 12, branch even though some variation in number occurred in a few of our experimental animals. Longitudinal sections of the appendix were used for histopathologic study.

EXPERIMENTAL EFFECTS OF LIGATION OF THE APPENDICAL VESSELS IN THE RABBIT

Ligation of the Main Appendical Artery and Vein and the Secondary Branches.

Rabbit 257.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery and vein just proximal to branch 7.

Period of observation: eight hours.

11. Huntington, G. S.: The Anatomy of the Human Peritoneum and Abdominal Cavity Considered from the Standpoint of Development and Comparative Anat., Philadelphia, Lea Bros. & Co., 1903.

Gross pathologic picture: There was hemorrhagic infarction of the distal portion of the appendix, with a striking, somewhat sinuous line of demarcation corresponding to the upper level of ligation. The lesion was segmental and appeared to involve chiefly the mucosa and submucosa. The serosa was apparently free from fibrin and purulent exudate. Distal segmental appendicitis was present.

Histopathologic picture: No sections were taken.

Rabbit 332.—Extent of occlusion: secondary branches 7, 8 and 9 and the main appendical artery and vein just proximal and distal to them.

Period of observation: nine hours.
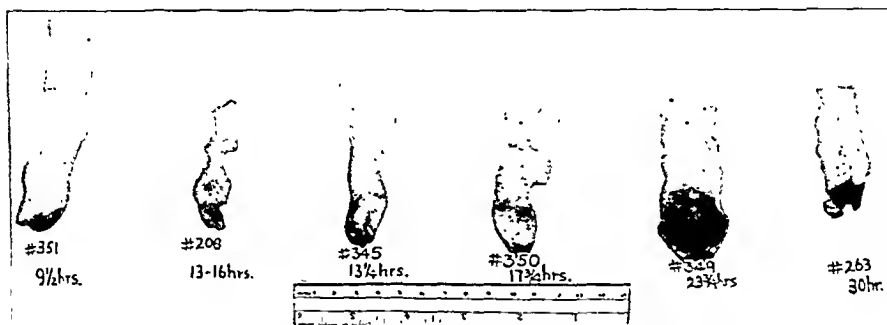
Fig. 2.—Experimental segmental appendicitis in the rabbit.
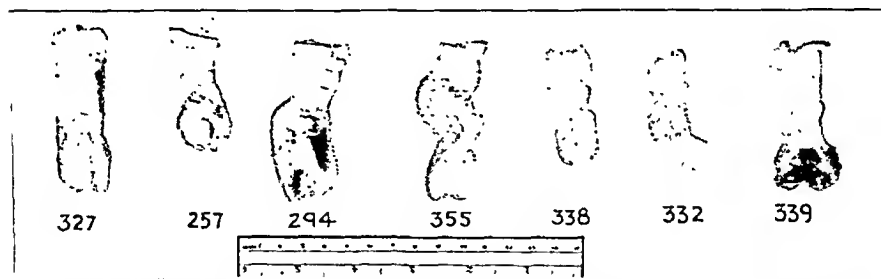
Fig. 3.—Experimental segmental appendicitis in the rabbit. Note the central lesion in the appendix of rabbit 332.

Gross pathologic picture: Immediately after ligation that portion of the wall directly opposite branches 7, 8 and 9 became cyanotic, the appendix distal to this area being mildly cyanosed. At the expiration of nine hours there were punctate and confluent hemorrhages, chiefly into the mucosa, which was clearly demarcated from the contiguous, normal-appearing pale tissue. The serosal vessels over the affected region were congested. The area of hemorrhagic necrosis corresponded to the distribution of secondary branches 7, 8 and 9. There was central segmental appendicitis.

Histopathologic picture: Longitudinal sections taken at the upper level of the junction of the diseased with the normal-appearing tissue revealed punctate hemorrhages into the mucosa, capillary congestion and extravasation of erythrocytes

into the subepithelial tissue. The lymph nodules were infiltrated with erythrocytes. The submucosa was edematous and contained numerous eosinophils and plasma cells.[12] The pathologic process appeared to be localized chiefly in the mucosa, in the form of punctate hemorrhagic necroses. The muscularis and the serosa were unaffected.

Rabbit 294.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein just proximal to branch 7.

Period of observation: ten hours.

Gross pathologic picture: The terminal segment of the appendix, corresponding to the distribution of the occluded vessels, was gangrenous. The entire wall was thickened and hemorrhagic up to and possibly including the serosa. The serosa was covered with a thin purulent exudate which extended for a short distance proximal to the line of demarcation. There was distal segmental appendicitis.

Histopathologic picture: No sections were taken.
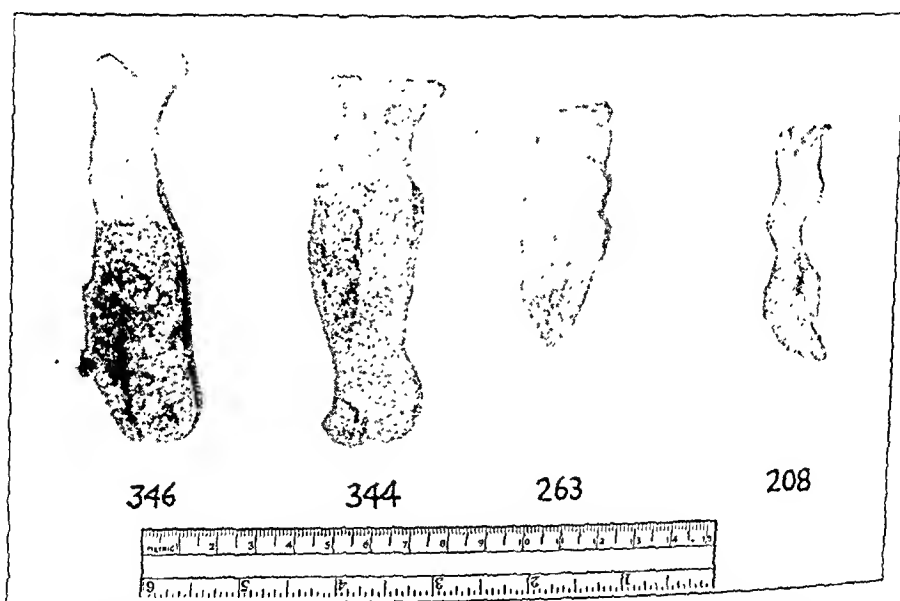
Fig. 4.—Experimental segmental appendicitis in the rabbit.

Rabbit 338.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein at points between branches 5 and 6 (ligature 1) and branches 8 and 9 (ligature 2).

Period of observation: eleven and one-half hours.

Gross pathologic picture: Immediately after application of ligature 2 the appendix distal to this point became deeply cyanotic. Between ligature 1 and ligature 2 the wall was midly cyanosed, gradually tapering off into normal tissue as a point opposite ligature 1 was reached. There apparently was maintenance of some blood supply through unligated secondary branch 6, probably through minute anastomoses with branch 5. At the end of eleven and one-half hours the proximal lesion, i. e., that between ligature 1 and ligature 2, consisted of punctate and

12. A moderate number of eosinophils and plasma cells are seen in the normal rabbit's appendix. Only definite increases above the average are noted in the protocol.

confluent hemorrhages apparently limited to the mucosa, with slight increase in thickness of the wall. The distal segment exhibited hemorrhagic necrosis of the mucosa, with more pronounced thickening of the wall than the proximal lesion.

Fig. 5 (rabbit 332, ligation nine hours).—Hemorrhagic necrosis of the mucosa, submucosa and lymph nodules. The muscularis and serosa (see arrow) are unaffected. Note the denudation of the mucosa overlying the enlarged lymph nodules.

The deeper layers were also involved, but to a lesser degree. The serosa was dull in appearance and was edematous. There was distal segmental appendicitis, with a proximal lesion of a lesser degree of severity.

Histopathologic picture: Longitudinal sections taken at the level of junction of the proximal and the distal lesion revealed marked hemorrhagic necrosis of the apexes of the lymph nodules and overlying mucosa, the latter being entirely necrotic. There appeared to be an increase in eosinophils and plasma cells in

Fig. 6 (rabbit 338, ligation eleven and one-half hours).—Hemorrhagic necrosis of the mucosa and of the apexes of the lymph nodules (see arrows).

the submucosa, which was also edematous. There was some cellular infiltration of the muscularis and serosa, with congestion of the serosal vessels. The histopathologic changes of the proximal segment were distinctly milder and of less extent than those seen in the distal segment.

Rabbit 336.—Extent of occlusion: secondary branches 6, 7, 8 and 9 and the main appendical artery and vein just proximal and distal to them.

Period of observation: seventeen hours.

Gross pathologic picture: The middle portion of the appendix, corresponding to the distribution of the ligated vessels, was completely necrotic. There was hemorrhagic infarction of the entire wall in this area, which was segmentally and sharply delineated at both ends from the contiguous, normal-appearing tissue. The serosa overlying the necrotic tissue was covered with a thin purulent exudate. The wall in the area of segmental involvement was approximately one and one-half times the thickness of the adjacent appendical tissue. Some mucus was present in the appendical lumen distal to the region of pathologic involvement, and the mucosal vessels were congested. There was central segmental appendicitis.

Histopathologic picture: Longitudinal sections taken at the line of demarcation between the grossly pathologic and the normal-appearing tissue revealed a more advanced process than that seen in rabbit 338. There were large areas of hemorrhagic necrosis in the centers of the lymph nodules and in the interstitial tissue between the nodules. The mucosa was necrotic, and there was rather diffuse infiltration of the submucosa, the muscularis and the serosa with polymorphonuclear eosinophils and neutrophils, which also permeated the narrow spaces between the lymph nodules. The nodules were large and exhibited reticulum cell hyperplasia. Scattered mononuclear cells and plasma cells were also seen in the submucosa, which was edematous. The histologic picture showed a strikingly clear line of demarcation from the adjacent intact tissue.

Rabbit 355.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery and vein (*a*) just above branch 6; (*b*) between branches 8 and 9.

Period of observation: seventeen hours.

Gross pathologic picture: Distal to ligature 2 there was complete gangrene of the wall. Between ligatures 1 and 2 the tissue appeared thickened and intensely red. The necrosis appeared to be more superficial and less advanced than in the area distal to ligature 2. There was a sharp line of demarcation at the point of ligature 1, although just proximal to it the mucosa was hyperemic. The difference in the extent of pathologic involvement between the two areas described appeared to be due to the preservation of branch 6. There was distal segmental appendicitis.

Histopathologic picture: No sections were taken.

Rabbit 339.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery and vein proximal to branch 9.

Period of observation: twenty-one hours.

Gross pathologic picture: The distal segment of the appendix, corresponding to the distribution of the ligated vessels, was completely gangrenous and covered by a thin purulent exudate which extended proximal to the clear line of demarcation. There were fresh adhesions to adjacent loops of intestine. There was distal segmental appendicitis.

Histopathologic picture: The entire wall was diffusely infiltrated with polymorphonuclear neutrophils and eosinophils. There was advanced hemorrhagic infarction, with coagulation necrosis involving the mucosa and submucosa and extending between the lymph nodules. The latter were for the most part in a state of partial or complete disintegration. Their centers exhibited areas of focal necrosis which were filled with polymorphonuclear cells and were bordered chiefly by eosinophils extending to the periphery of each nodule. There was a

clear line of demarcation of the gangrenous from the contiguous intact tissue, but the inflammatory infiltration extended into the latter for some distance in the muscularis and serosa. In this region the mucosa, the lymph nodules and the interstitial tissue were entirely unaffected and contained only scattered eosinophils

Fig. 7 (rabbit *327*, ligation twenty-seven hours).—Photomicrograph showing the mucosa and most of the lymph follicles sloughed off in the gangrenous area.

as normally seen in the rabbit's appendix. The area of acute inflammation and necrosis was almost twice as thick as the region of infiltration of the muscularis and serosa, with normal mucosa and lymph nodules.

Rabbit 327.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery and vein proximal to branch 9.

Period of observation: twenty-seven hours.

Gross pathologic picture: There was gangrene of the distal segment which had been supplied by the occluded vessels. The wall was grayish black and thin owing to sloughing off of part of the necrotic tissue. In this area the lumen appeared slightly bulbous. A thick purulent exudate covered the serosa and extended beyond the clear line of demarcation to the contiguous nongangrenous area. Distal segmental appendicitis was present.

Histopathologic picture: The tissue changes were similar to those described for rabbit 339 (ligation, twenty-one hours) except that they were more advanced. Part of the acutely inflamed and gangrenous area had sloughed off, leaving this portion of the wall approximately one-half the thickness of the nongangrenous area adjoining. The latter, however, exhibited infiltration of the muscularis and serosa with inflammatory cells, the mucosa, the lymph nodules and the interstitial tissue being entirely unaffected.

Ligation of the Main Appendical Artery and the Secondary Vessels.

Rabbit 351.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 8.

Period of observation: nine and one-half hours.

Gross pathologic picture: There was sharply segmental hyperplasia of the lymph nodules, corresponding to the distribution of the ligated vessels. The lymph nodules projected prominently above the general level of the mucosa, appearing as pale elevations encompassed at their bases by salmon pink areas of injected vessels. The serosa was edematous and presented a delicate network of vessels, which appeared to be empty. There was early distal segmental appendicitis with lymphoid hyperplasia.

Histopathologic picture: The lymph nodules were elongated and projected prominently into the mucosa, which was denuded in places where it covered the follicles (fig. 5). The follicles exhibited hyperplasia and some eosinophilic infiltration, the latter extending into the interfollicular stroma. The submucosa, the muscularis and the serosa were edematous and infiltrated with polymorphonuclear neutrophils and eosinophils. There was some infiltration of the muscularis and the serosa by these cells for a distance beyond the visible area of hyperplasia of the lymph nodules.

Rabbit 208.—Extent of occlusion: secondary branches 9, 10, 11 and 12 and the main appendical artery proximal to branch 9.

Period of observation: thirteen to sixteen hours.

Gross pathologic picture: There was distal segmental hemorrhagic necrosis affecting principally the mucosa and the submucosa, corresponding in extent to the distribution of the ligated vessels. The serosa appeared uninvolved.

Histopathologic picture: Sections taken so as to include tissue from either side of the line of demarcation revealed necrosis of the mucosa, edema of the lymph nodules and infiltration of the serosa with polymorphonuclear neutrophils and round cells. The pathologic process was chiefly confined to the mucosa and submucosa. Sections taken near the tip of the appendix revealed a more advanced and deeper necrosis, with infiltration of the serosa by inflammatory cells. The muscularis appeared to be only slightly involved, its condition seeming out of proportion to the advanced pathologic change discernible in the other layers. There was marked vascular congestion.

Rabbit 350.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 8.

Period of observation: seventeen and three-quarters hours.

Gross pathologic picture: There was a segmental area of hemorrhagic necrosis apparently limited to the mucosa and part of the submucosa, corresponding in
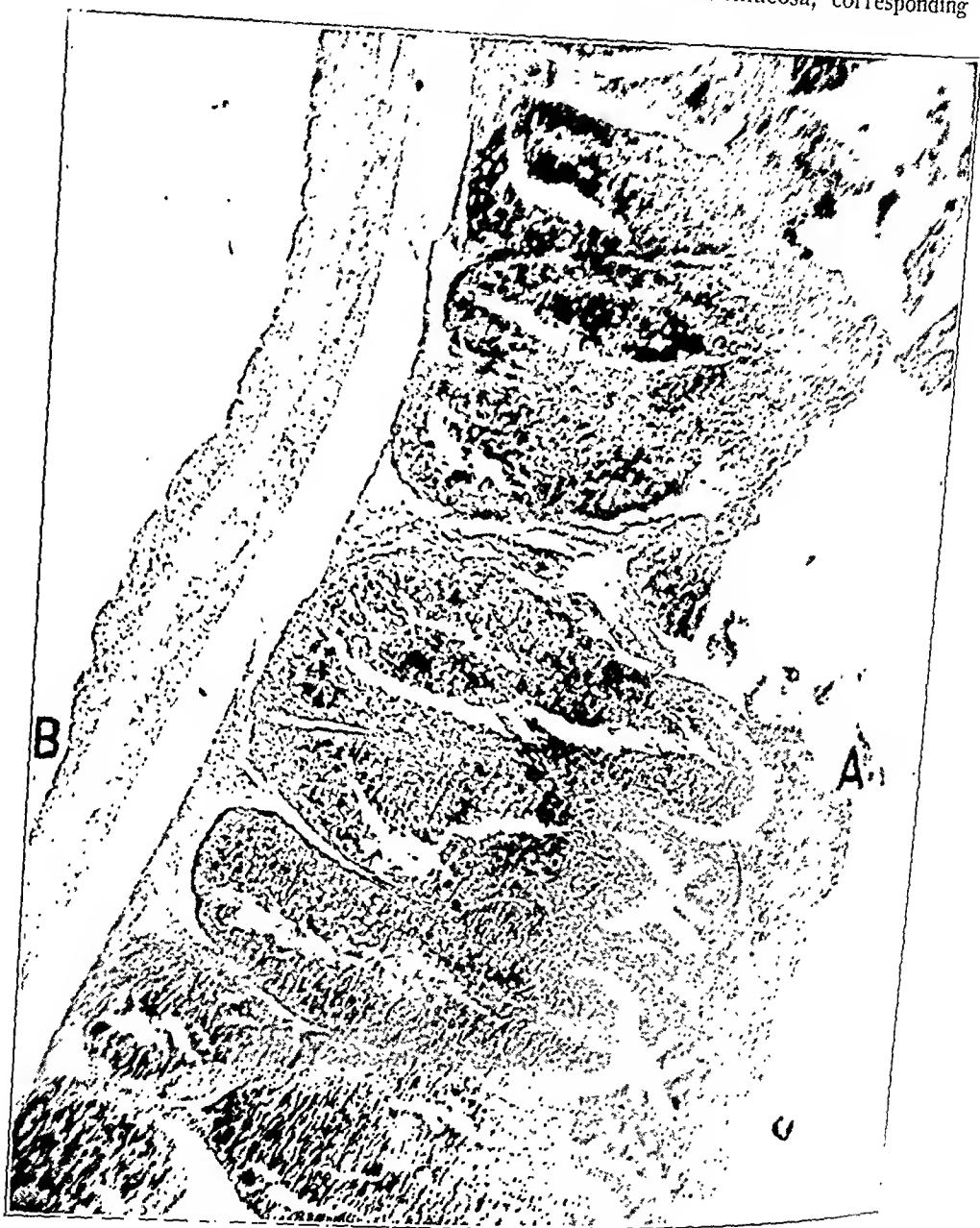
Fig. 8 (rabbit 327, ligation twenty-seven hours).—Edge of the segmental area of necrosis (*A*), showing the abrupt transition from uninvolved tissue; serosal involvement (*B*) beyond the edge of the segmental area of necrosis.

extent to the distribution of the ligated vessels. The serosa was ischemic, the arterial arborizations being devoid of blood. Distal segmental appendicitis was present.

Histopathologic picture: Longitudinal sections taken from the grossly involved area revealed hemorrhagic necrosis of the mucosa, edema and infiltration by neutrophils, eosinophils and plasma cells. Sections taken from a grossly uninvolved area a short distance above the line of demarcation showed no essential pathologic change.

Rabbit 349.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 12.

Period of observation: twenty-three and three-quarters hours.

Gross pathologic picture: The serosa was covered with a thin purulent exudate for a short distance proximal to the line of demarcation which indicated the extent of hemorrhagic necrosis of the distal segment. The necrotic area corresponded to the distribution of the ligated vessels. The pathologic process appeared to be limited to the mucosa. Distal segmental appendicitis was present.

Histopathologic picture: The changes were practically identical with those seen in rabbit 263 (ligation, thirty hours) except that they were slightly less advanced.

Rabbit 263.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical artery proximal to branch 7.

Period of observation: thirty hours.

Gross pathologic picture: There was a segmental area of complete gangrene involving the portion of the appendix which had been supplied by the occluded vessels. The major and distal portion had sloughed off at a point 1 cm. from the line of demarcation, leaving only a small fragment of necrotic appendix attached to the intact portion. The serosa of the attached fragment was covered with purulent exudate which extended proximally for a short distance. The entire area of distal segmental appendicitis was completely walled off by the surrounding coils of the intestine and mesentery. The peritoneum contained a small amount of sanguineous fluid.

Histopathologic picture: Longitudinal sections taken at the point of junction of the attached necrotic tissue and the normal-appearing appendix revealed edema of the entire wall, coagulation and hemorrhagic necrosis of the mucosa, submucosa and lymph nodules. There was diffuse infiltration of the muscularis and serosa by inflammatory cells, without marked necrosis. As healthy tissue was approached there appeared some areas of punctate hemorrhagic necrosis within the lymph nodules, followed by interstitial hemorrhages which outlined the nodules clearly. No other pathologic change was discernible.

Ligation of the Main Appendical Vein and the Secondary Vessels.

Rabbit 292.—Extent of occlusion: secondary branches 7, 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 7.

Period of observation: twenty-three and one-half hours.

Gross pathologic picture: The distal segment of the appendix which had been supplied by the occluded vessels was filled with coagulated blood. The wall was approximately three times the normal thickness, and a purulent exudate covered the serosa proximal to the line of demarcation.

Histopathologic picture: No sections were taken.

Rabbit 346.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 8.

Period of observation: twenty-four hours.

Gross pathologic picture: The distal segment which had been supplied by the occluded vessels was the seat of a clearly defined area of infarction which

involved the entire wall. The latter was covered with a thin purulent exudate and appeared to be three or four times the normal thickness. There were liquid and coagulated blood in the lumen of the appendix, chiefly beyond the line of demarcation. Distal segmental appendicitis was present.

Histopathologic picture: The picture was much like that seen in the appendix of rabbit 263. There was a well defined line of demarcation which separated the healthy from the diseased tissue. In the necrotic segment the lymph nodules exhibited central areas of hemorrhagic necrosis, and the entire wall showed infarction and infiltration by polymorphonuclear cells. The zone of hemorrhagic necrosis gradually lessened as healthy tissue was approached, giving way to perinodular hemorrhages and finally to normal lymph follicles. The serosa showed an infiltrate of neutrophils, which extended for some distance into the grossly uninvolved area.

Rabbit 344.—Extent of occlusion: secondary branches 8, 9, 10, 11 and 12 and the main appendical vein proximal to branch 8.

Period of observation: twenty-five hours.

Gross pathologic picture: The entire wall was the seat of hemorrhagic necrosis corresponding in extent to the distribution of the vessels occluded. The wall was thickened in this area, and a small amount of free blood was seen in the lumen.

Histopathologic picture: No sections were taken.

Ligation of the Main Appendical Artery, the Main Appendical Artery and Vein and the Secondary Vessels.

Rabbit 345.—Extent of occlusion: secondary branches 5, 6, 7, 8, 9, 10, 11 and 12, the main appendical artery proximal to branch 5 (ligature 2) and the main appendical artery and vein between branches 10 and 11 (ligature 1).

Period of observation: thirteen and one-quarter hours.

Gross pathologic picture: Between ligatures 1 and 2 the appendical wall was ischemic and pale, the mucosa exhibiting some hemorrhage and pinpoint areas of necrosis. Beyond ligature 1 the tip of the appendix was black and completely necrotic. In the area distal to the point of ligation of the artery (ligature 2) necrosis was less advanced and more superficial than in the area distal to the point of ligation of both artery and vein (ligature 1). A clear line of demarcation separated the latter from the former, which, in turn, was somewhat less sharply demarcated from contiguous uninvolved tissue. Graded segmental appendicitis was present.

Histopathologic picture: The microscopic picture resembled that seen in rabbit 208 (approximately the same period after ligation of the main artery and secondary branches). Longitudinal sections taken from the necrotic tip of the appendix revealed involvement of all coats. The mucosa was completely necrotic; the lymph nodules were likewise involved at their upper poles; there was edema of the submucosa, and all coats, including the serosa, were infiltrated by polymorphonuclear cells.

Rabbit 333.—Extent of occlusion: secondary branches 9, 10, 11 and 12, the main appendical vein between branches 7 and 8 and the main appendical artery and vein proximal to branch 4.

Period of observation: twenty-four hours.

Gross pathologic picture: The extreme distal segment of the appendix was the seat of hemorrhagic necrosis corresponding to the distribution of the occluded secondary branches. The vascular supply of the proximal portion of the appendix appeared to have been maintained by the secondary branches above branch 9,

through the vessel which coursed behind the ileum. Ligation of the main appendical artery and vein proximal to branch 4 was apparently compensated for by this arrangement.

Histopathologic picture: No sections were taken.

Temporary Occlusion of the Main Appendical Artery and Vein with Ligation of the Secondary Branches.

Rabbit 340.—Extent of temporary occlusion: secondary branches 9, 10, 11, 12 ligated and main appendical artery and vein temporarily occluded proximal to branch 9.

Duration of occlusion of the main vessels: fourteen minutes' interruption, four minutes' release, ten minutes' reinterruption and then permanent reestablishment of circulation. The appendix was examined twenty-three hours later.

Gross pathologic picture: The appendix was taut, being distended with sanguineous material within the lumen. The contents were under increased pressure. The wall showed no gross pathologic change except at the extreme tip of the appendix where there was an area of focal necrosis measuring 0.5 cm. in diameter. This observation suggests the importance of the secondary branches in maintaining an adequate blood supply to the wall of the appendix.

Ligation of the Appendical Wall and Distention with Fluid.

Rabbit 374.—In this experiment the vessels were not ligated. Two sutures were placed at points about the proximal and distal thirds of the appendix, thus forming two closed sacs. Two cubic centimeters of sterile saline solution was injected into the lumen of the distal segment and 5 cc. into the lumen of the proximal segment. The pulsations in the main appendical artery disappeared almost immediately, and the organ appeared distended and pale. Nineteen and one-half hours later the serosa covering both sacs was covered by a thick purulent exudate. The appendix remained distended, and punctate areas of hemorrhagic necrosis were seen in the mucosa. It seemed probable that the pathologic involvement was due essentially to mechanical interference with the blood supply by distention and subsequent pressure on the wall, since absence of pulsation was noted immediately after the injection of saline solution. A possible but unlikely source of error is infection along the track of the hypodermic needle since this generally produces a more localized type of peritonitis.

Rabbit 348.—A single ligature was tried about a point at approximately the distal third of the appendix. Eight and five-sixths days later the appendix distal to the ligature appeared ruptured and gangrenous, and a localized abscess surrounded the remaining stump. Generalized peritonitis was present.

SUMMARY OF EXPERIMENTAL OBSERVATIONS

1. Ligation of the main vessels and secondary branches was followed by a sharply segmental type of appendical necrosis which, in general, corresponded to the distribution of the occluded vessels.

2. The degree and severity of the subsequent pathologic process depended on the extent of the vascular block and the duration of occlusion.

3. There appeared to be little difference in the results whether the main artery and vein were ligated singly or concomitantly with the secondary branches, except that a more hemorrhagic type of infarction

with free intraluminal blood was seen when the vein alone was occluded in addition to the secondary vessels.

4. The earliest segmental changes noted (eight to nine hours) were limited to the mucosa and submucosa. At ten hours the serosa was covered with purulent exudate.

5. Complete gangrene with sloughing of the affected segment occurred in approximately twenty-four hours after vascular occlusion.

6. Microscopic evidence of lateral extension of the inflammatory process beyond the line of demarcation was usually limited to the serosa, the overlying coats being unaffected.

7. The area of intramural spread of infection was wedge shaped, the base of the wedge being formed by the serosa.

COMPARATIVE STUDIES OF ACUTE SEGMENTAL APPENDICITIS IN MAN

Twenty cases of human segmental appendicitis have been chosen to illustrate the proximal, central and distal types of involvement. This division is only approximate since many specimens exhibit involvement of two contiguous segments. We have on rare occasions encountered a "skip" type in which the proximal and distal portions are involved and the central segment is intact.

The general frequency of the segmental type of involvement is suggested by the incidence of 17.5 per cent in our series of 200 cases of acute appendicitis.

The distribution of the cases with relation to age and sex was as follows:

		Decade				
Sex		1	2	3	4	5
Male 13		0	5	4	3	1
Female 7		2	3	1	1	0

Gross Pathologic Observations.—The gross pathologic findings are arranged in order of the duration of symptoms before the appendix was removed.

The duration of symptoms prior to operation varied from ten to forty-eight hours.

1. A woman aged 22 had had symptoms for ten hours. The appendix was 5 cm. in length. The serosal vessels were injected and the serosa was covered with a thin purulent exudate. The mucosa in the distal third was hemorrhagic and exhibited follicular ulceration. There was a clear line of demarcation separating this area from the adjacent tissue.

2. A boy aged 14 had had symptoms for ten hours. The appendix was 8 cm. in length. The serosa over the proximal two thirds was covered with purulent exudate. The segmental involvement was clearly apparent externally as well as

on the inner aspect, where the mucosa was hemorrhagic and ulcerated. The unopened appendix was dilated and tense in this area, and a fecalith was present.

3. A boy aged 11 had had symptoms for ten hours. The appendix was 10 cm. in length. The distal 6 cm. of serosa was covered with a purulent exudate, cor-

1-3 arteries, supplying
  only appendix.
Origin:
    ileocolic
    posterior ileocecal
    anterior ileocecal
    mesenteric branch of ileocolic

1-3 arteries to appendix,
  proximal branch supplying
  portion of cecum.
Origin:
    ileocolic
    posterior ileocecal
    anterior ileocecal
    mesenteric branch of ileocolic

Two arteries form
  ing a loop in
  mesoappendix
  from which in-
  dividual branches
  arise.

Fig. 9.—Vascular supply of the human appendix.
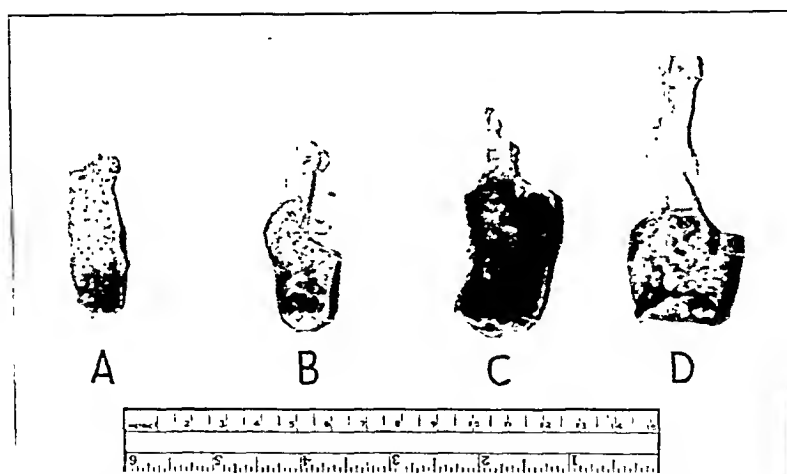
Fig. 10.—Human segmental appendicitis (*A*) in case 1, with symptoms of ten hours' duration, (*B*) in case 11, with symptoms of twenty-one hours' duration, (*C*) in case 6, with symptoms of fifteen hours' duration, and (*D*) in case 19, with symptoms of thirty-two hours' duration.

responding in its extent to underlying sharply segmental hemorrhagic necrosis of the mucosa. The wall was thickened in this area and the lumen slightly bulbous.

4. A man aged 25 had had symptoms for twelve hours. The appendix was 6 cm. in length. The serosal surface was covered with a thin purulent exudate,

most marked at the tip of the appendix. The wall was thickened and bulbous in the distal third, where the mucosa was the site of sharply segmental hemorrhagic necrosis.

5. A man aged 27 had had symptoms for thirteen hours. The appendix was 9 cm. in length. The lumen was filled with pus, and many fecaliths were present in the distal half, where the mucosa was necrotic. The serosal vessels were injected near the tip. It is of interest to note that at operation the appendix was distorted into the shape of the letter V owing to adhesions.

6. A man aged 31 had had symptoms for fifteen hours. The appendix was 7 cm. in length. The serosa was covered with a purulent exudate in its distal two thirds, where the wall exhibited a clear line of demarcation. The mucosa exhibited hemorrhagic infarction in the distal 6 cm., and the lumen was filled with liquid feces and fecaliths.

7. A girl aged 7 years had had symptoms for sixteen hours. The appendix was 7 cm. in length. The serosa in the distal half was covered with a purulent exudate. The wall in this area was thin owing to segmental hemorrhagic infarction and sloughing of the mucosa. At operation it was noted that in the region of distal segmental appendicitis the organ was distended and tense, and at the line of demarcation the lumen was obstructed by a fecalith.

8. A girl aged 15 had had symptoms for eighteen hours. The appendix was 6 cm. in length. The serosa in the distal third was covered with a thick purulent exudate, and corresponding to the location and extent of this condition there was a clearly segmental area of hemorrhagic necrosis on the mucosal surface.

9. A man aged 34 had had symptoms for eighteen hours. The appendix was 5 cm. in length. The serosa was covered with a thin purulent exudate. The wall was thickened, and the mucosa was hemorrhagic and necrotic in the middle third.

10. A man aged 50 had had symptoms for twenty-one hours. The appendix was 7 cm. in length. The serosa was covered with a thin plastic exudate in its middle third. The mucosa exhibited a segmental area of hemorrhagic necrosis in the distal half, where the wall was distinctly thickened. Several small intramural leiomyomas were present.

11. A man aged 26 had had symptoms for twenty-one hours. The appendix was 6 cm. in length. The entire wall in the central 3 cm. was the seat of hemorrhagic necrosis. In this area the wall was thinned and the mucosa sloughed off. The lumen in the distal 1 cm. was obliterated. At operation the appendix was found sharply angulated.

12. A woman aged 37 had had symptoms for twenty-two hours. The appendix was 6 cm. in length. The serosa was covered with a purulent exudate, and the mesenteriolar fat was thickened and indurated. The appendical wall was thickened and necrotic in its distal two thirds.

13. A girl aged 19 had had symptoms for twenty-four hours. The appendix measured 8 cm. in length. The serosa was covered with a thin purulent exudate. The wall was thin and necrotic in almost its entire length. The lumen contained several fecaliths.

14. A man aged 33 had had symptoms for twenty-four hours. The appendix was 8 cm. in length and curled to the shape of a letter U. The serosa of the distal 5 cm. was covered with a thin purulent exudate. There was segmental necrosis of the entire wall in this area, with a clear line of demarcation on the

mucosal surface. The involved portion of the canal was bulbous and contained several soft fecaliths and purulent material under slightly increased pressure. There were two vessels in the attached mesenteriolum, which appeared to be thrombosed. At a point 2 cm. from the proximal end there was stenosis of the lumen.

15. A man aged 29 had had symptoms for twenty-four hours. The appendix was 5 cm. in length. The serosa was covered with a purulent exudate, and the wall was gangrenous in its middle third, with a clear line of demarcation on either side. Mural thickening extended for a short distance beyond the area of segmental involvement.

16. A youth aged 19 had had symptoms for twenty-four hours. The appendix was 5 cm. in length. The serosa was covered with a plastic exudate in the distal two thirds. The wall was thickened throughout its length, and the distal half exhibited segmental hemorrhagic necrosis.

17. A youth aged 19 had had symptoms for twenty-four hours. The appendix was 7 cm. in length. The serosa was covered with a thin purulent exudate in the distal third. In this area the wall was thin, necrotic and pitted. with a clear line of demarcation at its junction with apparently normal tissue.

18. A girl aged 5 years had had symptoms for twenty-five and one-half hours. The appendix was 7 cm. in length. The wall was necrotic in its distal half, and the serosa was covered with a purulent exudate. There was a clear line of demarcation at the proximal end of the involved area.

19. A boy aged 12 had had symptoms for thirty-two hours. The appendix was 8 cm. in length. The distal third was the seat of segmental hemorrhagic necrosis and over this area the serosa was covered with a purulent exudate. The wall was thinned owing to the casting off of a gangrenous slough.

20. A girl aged 16 had had symptoms for forty-eight hours. The appendix was 6 cm. in length. The serosa was covered with a thick purulent exudate, and the wall was completely necrotic in the distal 5 cm. The mucosal aspect exhibited a sharply segmental area of involvement in the same location with advanced sloughing. Here the wall was thin and the lumen bulbous. There was a fecalith at the proximal line of demarcation.

Histologic Observations.—The general microscopic picture of acute segmental appendicitis in man follows closely the changes associated with the same condition in the rabbit. The early lesions are superficial and are limited chiefly to the mucosa and lymph nodules. The intramural spread of infection follows the general direction of the submucosal, intramuscular and intermuscular lymphatic networks until it reaches the serosa. It is wedge shaped and resembles the process of lymphatic extension in carcinoma of the bowel. The mucosal lesion is usually much smaller in extent than the serosal area of inflammation. The line of demarcation visible in the gross specimen exhibits the same sharply segmental type of necrosis in both rabbit and man. The time necessary for the production of complete necrosis of the appendix appears to be somewhat shorter in man than in the experimental animal. The discrepancy may be due. however. to the difficulty of establishing the exact time of onset of pathologic involvement.
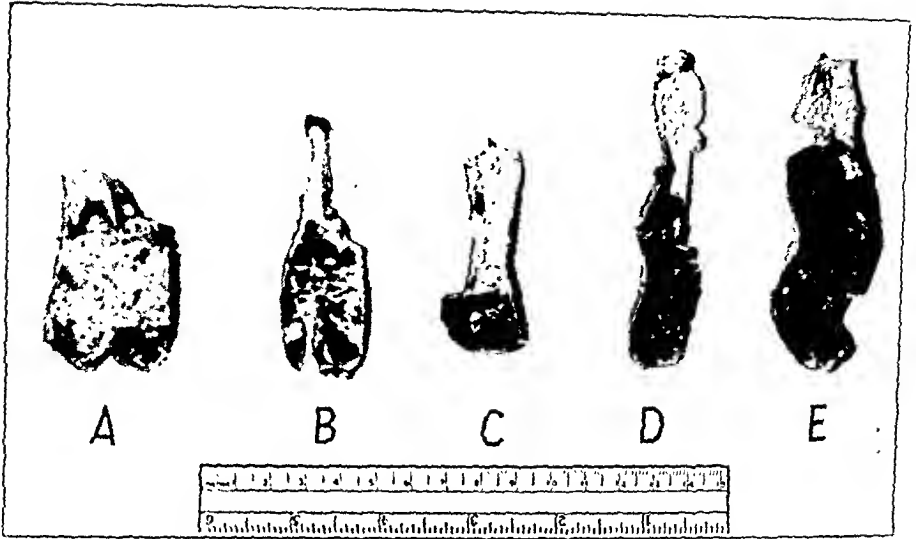
Fig. 11.—Human segmental appendicitis (*A*) in case 20, with symptoms of forty-eight hours' duration, (*B*) in case 2, with symptoms of ten hours' duration, (*C*) in a case not included in this report, with symptoms of forty-eight hours' duration, (*D*) in case 14, with symptoms of twenty-four hours' duration, and (*E*) in case 3, with symptoms of ten hours' duration.
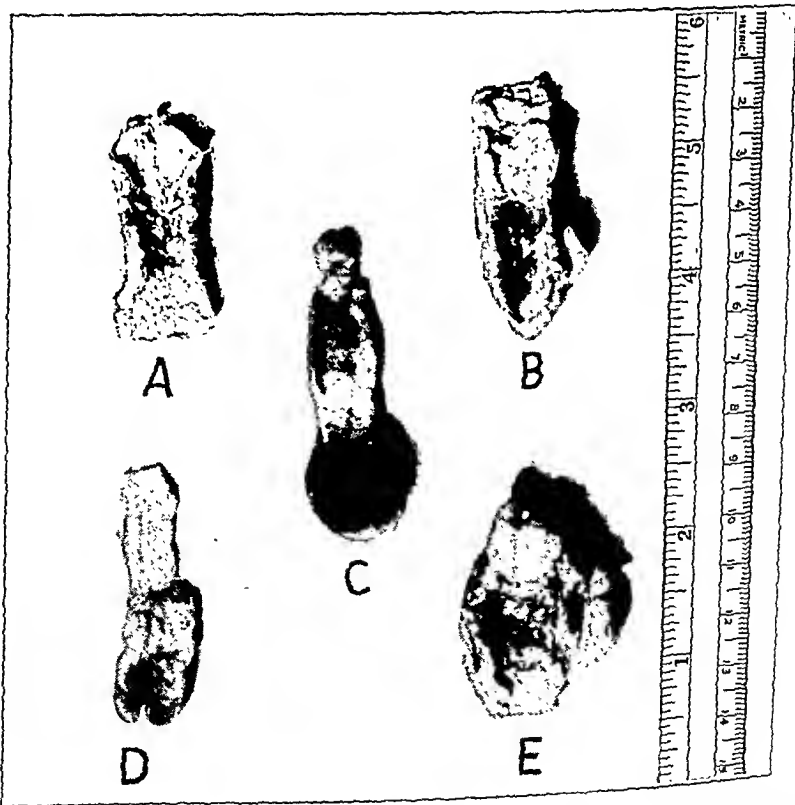
Fig. 12.—Human segmental appendicitis (*A*) in case 15, with symptoms of twenty-four hours' duration, (*B*) in case 16, with symptoms of twenty-four hours' duration, (*C*) in case 4, with symptoms of twelve hours' duration, (*D*) in case 9, with symptoms of eighteen hours' duration, and (*E*) in case 18, with symptoms of twenty-five and one-half hours' duration.

CORRELATION OF EXPERIMENTAL AND CLINICAL DATA

From an anatomicopathologic standpoint there are two obvious points of similarity between segmental appendicitis in the rabbit and the same condition in man. First, the vascular supply in both is of the terminal type. Second, the clearly defined segmental lesions produced by vascular ligation in the rabbit resemble both grossly and microscopically those

Fig. 13.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. The section was taken at the line of demarcation. Note the abrupt loss of continuity of the epithelium at the edge of the necrotic area.

observed in man. The possible point of divergence lies in the pathogenesis. Are all segmental lesions in the human appendix due to vascular occlusion? If so, what is the etiologic explanation? Is there any relation to acute appendicitis in general? It is difficult to answer these

three questions with any degree of finality unless primary vascular occlusion can be proved to have occurred in each case. This necessitates careful taking of clinical histories, detailed observations by the surgeon
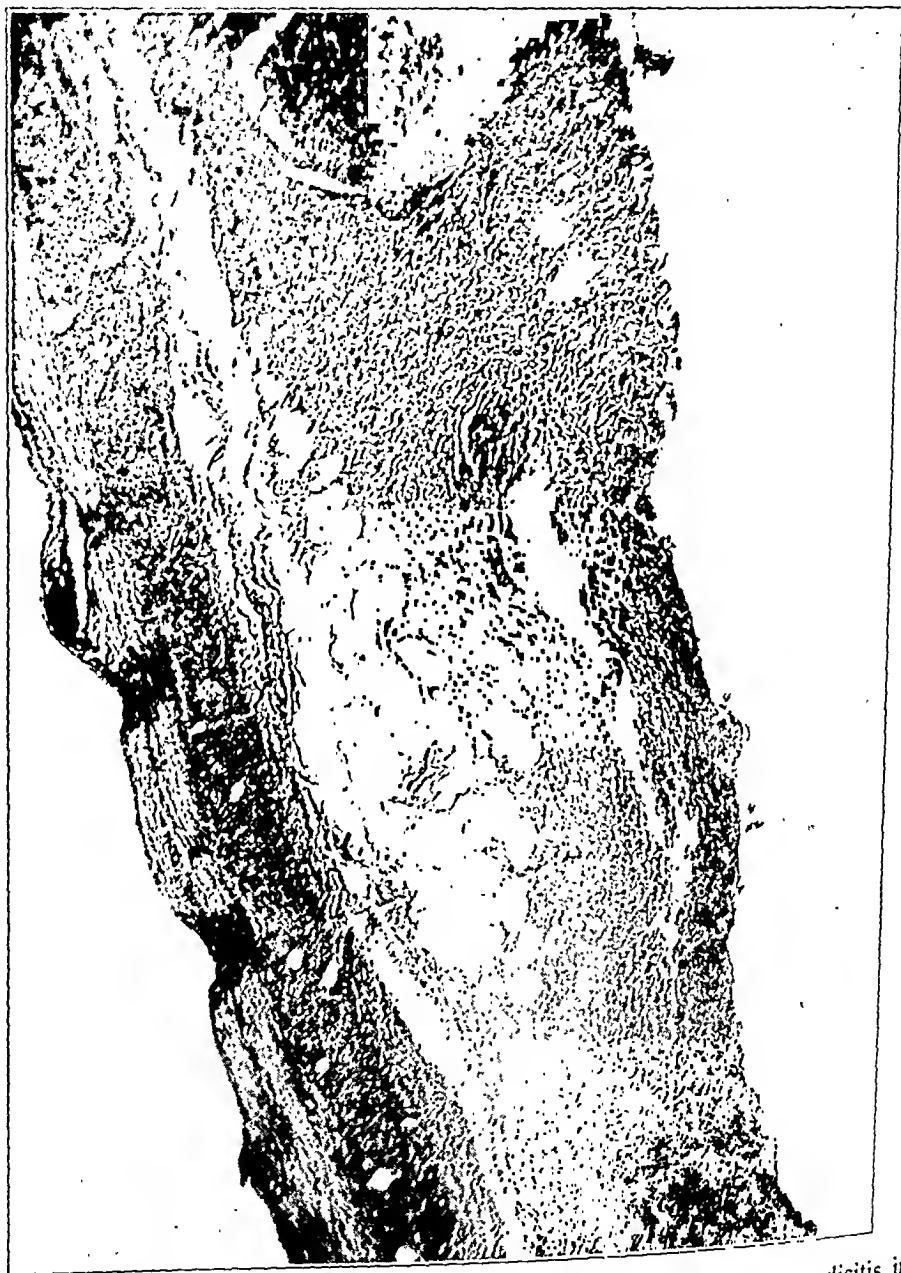
Fig. 14.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. The section was taken at the line of demarcation. Note the intact lymph follicle at the top. The overlying epithelium is partly preserved and at the extreme bottom completely necrotic, together with the underlying mucosa.

and elimination of the possibility that vascular involvement may follow acute appendicitis instead of preceding it. Many divergent opinions

have been offered regarding the genesis of acute appendicitis. We shall attempt to reconcile these views with our hypothesis that acute segmental appendicitis in man is due to vascular occlusion.

Aschoff has postulated that acute appendicitis begins as a superficial localized lesion of the epithelium of the appendix, with the formation of a plug of leukocytes in a fold of the mucosa, usually in the distal portion. From this point there occurs a wedge-shaped spread to the

Fig. 15.—Photomicrograph (× 20) showing human segmental appendicitis in a case not included in this report. There is superficial necrosis. Note the rather sharp line of demarcation. In this region the mucosa and the lymph nodules are necrotic.

other coats, which are apt to be more extensively involved than the primary focal area. Aschoff further stated that the causative infecting organisms are brought to the appendix by the enterogenous route. These bacteria are apt to be gram-positive organisms, particularly diplococci and slender bacilli which Aschoff has admitted are normally present in the appendix. No explanation is offered as to why these normal inhabi-

tants suddenly acquire invasive tendencies. It is difficult to comprehend how an organ which is normally laved by pathogens or potential pathogens can be suddenly invaded unless some other factor becomes operative which permits intramural penetration.[13] It is probable that Aschoff's enterogenic theory and his description of the histopathologic process are correct up to the point of intramural invasion. If necrosis of the mucosa by direct contact of bacteria is the sole explanation of acute appendicitis it is difficult to explain acute mural involvement of an obliterated appendix in which no mucosa is seen. We have noted several such instances. Indirect evidence is presented by pharyngogenic hematogenous streptococcic peritonitis [14] and chronic bacillary dysentery. In the former disease foci of hemorrhagic intestinal necrosis has been noted in man and reproduced in the rabbit by intravenous injection of the organisms recovered from the throat. The intestinal lesions are secondary to the direct action of streptococci or their toxins on the mesenteric vessels within the wall of the intestine during the process of excretion from the blood stream into the lumen of the bowel and so out of the body. Nordlund [15] stated that in man there is a transient invasion of the blood stream by organisms from a primary focus in the throat. We believe that involvement of the peritoneum occurs through the areas of necrosis described, particularly since intramural penetration is indicated by the isolation of streptococci and of Bacillus coli from the peritoneal exudate. A case may be cited, that of a child, in which three separate areas of focal hemorrhagic necrosis occurred in the appendix, and on each was found a drop of greenish pus from which was isolated the same streptococcic strain as was present in the throat. In chronic bacillary dysentery [16] the primary ulcerative lesions are produced in the acute phase during the process of excretion of the dysentery toxin from the blood into the lumen of the bowel. The intestinal lesions can be reproduced by intravenous injection of the dysentery toxin alone. Secondary, nonspecific intramural invasion, particularly by enterococci and by B. coli, occurs during the chronic stage through the ulcers originally produced by the dysentery toxin. In one form of acute bacillary dysen-

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13. Felsen, J.: Acute and Chronic Bacillary Dysentery, Am. J. Path. **12:**395 (May) 1936.

14. Felsen, J., and Osofsky, A. G.: Pharyngogenic Hematogenous Streptococcic Peritonitis, Arch. Surg. **31:**437 (Sept.) 1935.

15. Nordlund, U.: Ueber die sogenannte primäre kryptogenetische oder metastatisch Streptokokken Peritonitis, Ann. Acad. sc. fenn. (ser. A), 1933, vol. 38, no. 1.

16. Felsen, J.: The Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Nonspecific Granuloma, Ann. Int. Med. **10:**645 (Nov.) 1936.

tery, the appendical type,[17] the mucosa of the entire appendix is actually the site of punctate follicular necrosis without the development of acute suppurative appendicitis. Resolution takes place in the usual seven to ten day period just as it does in the ileum and colon. In the chronic stage it has been possible to demonstrate ulceration of the colon, ileum and appendix without evidence of acute appendicitis. The recent work of Altemeier,[18] who studied the bacterial flora in cases of acute perforating appendicitis, adds further doubt to the contention that the normal appendical bacteria, particularly B. coli and Enterococcus, can cause appendicitis without previous preparation by other factors. We therefore feel, as do other investigators, that there must be some additional agent which prepares the mucosal field before organisms normally present in the appendix can invade its wall. What is this factor?

Ricker [19] suggested that appendicitis begins as a circulatory disturbance of nervous origin which results in hemorrhagic infarction of the mucosa, through which a portal of entry is afforded the intraluminal bacteria. In mild involvement no appreciable lesion is produced, but in severe involvement necrosis of the mucosa occurs, secondary invasion of bacteria follows and gangrene results. Longhitano [20] stated the opinion that every acutely inflamed appendix previously has been the seat of a hematogenous embolic lesion. Surgeons have frequently noted thrombosed vessels in the mesenteriolum, with gangrene of the appendix below the point of obstruction.[21] They are commonly detected as the vessels are cut across, because no bleeding occurs. Various investigators have attempted to produce experimental appendicitis in rabbits by hematogenous or vascular occlusion. Beaussevat [22] concluded that while the disease can be produced by infection of the blood or of the lymph stream it is more commonly due to infection from the intestinal tract. Josue [23] produced appendicitis in rabbits by the intravenous injection of

17. Felsen, J.: Appendicular Form of Bacillary Dysentery, with Notes on Mesenteric Adenitis and Inflammation of the Distal Portion of the Ileum, Am. J. Dis. Child. **50**:661 (Sept.) 1935.

18. Altemeier, W. A.: The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis, Ann. Surg. **107**:517 (April) 1938.

19. Ricker, G.: Der Stand der Lehre von der Epityphilitis, Deutsche Ztschr. f. Chir. **202**:125, 1927.

20. Longhitano, A.: La morphologia e la patologia del appendice vermiforme. Milano, A. Cordani, 1928; cited by Aschoff, L.: Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., Ltd., 1931.

21. Royster, H. A., in discussion on Wangensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W.: Studies in the Etiology of Acute Appendicitis, Ann. Surg. **106**:910 (Nov.) 1937.

22. Beaussevat, M.: Appendicitis expérimentales, Rev. de gynéc. et de chir. abd. **1**:283, 1897.

23. Josue, O.: Appendicites. expérimentales par infection sanguine, Compt. rend. Soc. de biol. **49**:280, 1897.

streptococci without previous traumatization of the mucosa. Muhsam[24] ligated the appendical vessels of rabbits and succeeded in producing peripheral necrosis. Brunn's work on the experimental production of segmental inflammatory lesions of the appendix has already been described.

The concept of appendicitis as a focal manifestation of systemic infection, usually by the hematogenous route, has been proposed by Tripier and Paviot,[25] Grant,[26] Finney and Hamburger,[27] Rosenow[28] and others. Antecedent tonsillitis has often been credited with etiologic importance.[29] The so-called epidemic type of appendicitis has been described, particularly that following infections of the upper part of the respiratory tract. While the possibility exists that the direct enterogenous route may be followed by the invading organisms, our work points to the indirect hematogenous mechanism as an important and hitherto neglected factor.[30] Toxins, bacteria and heavy metals are excreted from the blood stream into the lumen of the bowel in this manner. Embolic lesions of the finer mesenteric radicals within the wall of the intestine are far commoner than thrombosis of the larger vessels. Toxins frequently act on the endothelium of the smaller blood vessels and produce necrosis with subsequent blockage. The chief route of excretion of lead from the blood stream is along the entire intestinal tract, with subsequent elimination in the feces. It is during this process of excretion of toxins and bacteria from the blood that the intramural structures are damaged and offer a focal point of entry for invading organisms. Intestinal lesions have been noted in association with many diseases, some of them possibly due to viruses. In addition to those previously referred to we would mention rheumatic intestinal necrosis, periarteritis nodosa and streptococcic, meningococcic, pneumococcic and staphylococcic bacteremias. The comparative rarity of acute appendicitis during intrauterine life and in newborn infants suggests the possibility of a protective immunizing mechanism transferred from the mother, which

24. Muhsam, R.: Ueber Appendicitisexperimente, Deutsche Ztschr. f. Chir. **55**:143, 1900.

25. Tripier, R., and Paviot, J.: L'appendicite par infection général, Semaine méd. **29**:73, 1899.

26. Grant, J.: Rare Forms of Gout and Rheumatism, Montreal M. J. **22**:341, 1893; M. Rec., New York **44**:609, 1893.

27. Finney, J. M. T., and Hamburger, L. P.: The Relationship of Appendicitis to Infectious Diseases, Am. Med. **2**:941 (Dec. 14) 1901.

28. Rosenow, E. C.: Bacteriology of Appendicitis and Production by Intravenous Injection of Streptococci and Colon Bacilli, J. Infect. Dis. **16**:240, 1915.

29. Relation of Tonsillitis to Appendicitis, 1893-1928, Bibliography 189, Library of the New York Academy of Medicine, Bibliographical Department, Oct. 23, 1928.

30. Felsen, J.: Intestinal Manifestations of Systemic Disease, Rev. Gastroenterol. **5**:114 (June) 1938.

appears to be operative against many diseases during this period. In the other extreme of life vascular occlusion may be due to organic changes associated with senility. Gatewood [31] stated that appendicitis in the aged is sometimes of embolic origin.

The relation of distention of the appendical lumen to acute appendicitis has been stressed by some investigators. Van Zwalenburg [32] occluded the appendical canal in the dog by means of a ligature and then injected fluid under high pressure. He concluded that when the "hydraulic pressure equal to the arterial tension is maintained within the lumen of the appendix for a short time it is promptly followed by typical appendicitis." The experimental studies of Wangensteen [33] and his co-workers along similar lines led them to conclude that distention is probably the most important factor in the production of experimental appendicitis. In carrying out the experiment of ligation of the appendical wall and distention with fluid on rabbit 374 we noted the almost instantaneous disappearance of pulsation in the main appendical artery. The natural assumption is that as a result of continued compression by the increased tension within the lumen the arterial supply was cut off and necrosis with infection of the involved segment followed. Bowers [34] concluded that acute appendicitis is a form of closed loop obstruction in the majority of cases. The appendix being essentially secretory, the segment obstructed distends and eventually ruptures. This possibility is illustrated by the appendixes in cases 2, 7, 14 and 20, in which either a stricture or a fecalith was observed at the line of demarcation.

The peculiar anatomic variations in the position of the human appendix and its rather free mobility render the theory of a mechanical vascular or luminal obstruction feasible. Twists or angulations by adhesive bands are conceivable (cases 5 and 11). Vascular obstruction may be only temporary, being due to a transient twist of the mesentery which would no longer be discernible at the time of operation. This is one of many difficulties which stand in the way of demonstrating conclusively the presence or absence of vascular occlusion in man. In some cases the surgeon makes no note of the presence or absence of thrombosed vessels, and insufficient mesenteriolum is supplied the pathologist to enable him to reach a definite conclusion. At times it is

31. Gatewood: Appendicitis in Old Age, M. Clin. North America **10**:303 (April) 1930.

32. Van Zwalenburg, C.: Obstruction and Consequent Distention the Cause of Appendicitis, as Proved by Cases and by Experimental Appendicitis in Dogs, J. A. M. A. **42**:820 (March 26) 1904.

33. Wagensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W.: Studies in the Etiology of Acute Appendicitis. Ann. Surg. **106**:910 (Nov.) 1937.

34. Bowers, W. F.: The Role of Distention in the Genesis of Acute Inflammation of Hollow Viscera, Am. J. M. Sc. **194**:205 (Aug.) 1937.

impossible to state whether the thrombosis is primary or secondary. Careful histories and search for primary foci are woefully lacking in cases of acute appendicitis, thus making it impossible to trace some antecedent factor. In only 2 of the cases reported in this series was a preceding infection of the respiratory tract observed (cases 7 and 15). It becomes necessary, therefore, to rely on experimental data and parallel observations on the intestine in the presence of other diseases. Whether the blood vessels are affected by systemic toxins or by bacteria from a distant focus or whether they are obstructed secondarily by distention of the lumen, by angulation or by foreign bodies, the theory of vascular occlusion as the cause of segmental appendicitis seems plausible. The applicability of this theory to the pathogenesis of appendicitis in general is also suggested by the data herein presented.

SUMMARY AND CONCLUSIONS

The general concept of segmental appendicitis is described.

Lesions similar to those seen in man have been produced in the rabbit by vascular occlusion.

An attempt has been made to reconcile the various theories regarding the cause of appendicitis with the theory of vascular occlusion, which we hold to be true in the case of acute segmental appendicitis.

INCARCERATED MECKEL'S DIVERTICULUM
IN FEMORAL HERNIA

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AND

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Johann Friedreich Meckel[1] was the first to describe a congenital diverticulum of the lower portion of the ileum. His description was published in 1808. He called attention to the importance of this structure in causation of serious disease. One hundred and fifteen years before this report, in 1683, Ruysch[2] had described a diverticulum and later in 1701 had published in "Thesaurus Anatomicus" (vol. 7, fig. 283) an illustration of this malformation. In 1700 Littré[3] reported a diverticulum encountered in a hernial sac. He, however, failed to describe the muscular coats characteristic of the congenital defect, and the embryonic derivation was not traced. It was from this description that the term "Littré's hernia" took origin.

Meckel's diverticulum, an anomaly found in man, occurs rather commonly. Various opinions have been expressed as to its incidence. The estimates range from 0.1 to 3 per cent. Balfour[4] found 15 Meckel's diverticula in 11,107 abdominal operations (0.1 per cent). Routine exploration, however, was not performed in this series. Cunningham in his "Textbook of Anatomy"[5] stated that Meckel's diverticulum was present in 73 of 3,302 cadavers (2.2 per cent). Schaetz[6] found 17 diverticula in 737 cadavers (2.3 per cent). In 10,300 necropsies,

1. Meckel, J. F.: Ueber die Divertikel am Darmkanal, Arch. f. d. Physiol. **9:**421-453, 1808.

2. Ruysch, cited by Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst. Med. Chicago **9:**286-308, 1933.

3. Littré, cited by Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst. Med. Chicago **9:**286-308, 1933.

4. Balfour, D. C.: Meckel's Diverticulum: A Report of Fifteen Cases, J. Minnesota State M. A. **31:**110-112, 1911.

5. Cunningham, D. J.: Textbook of Anatomy, ed. 5, New York, William Wood & Company, 1923, p. 1200.

6. Schaetz, G.: Beiträge zur Morphologie des Meckel'sche Divertikels, Beitr. z. path. Anat. u. z. allg. Path. **74:**115-293, 1925.

Turner [7] found 81 (0.8 per cent). Forque and Riche [8] noted 112 in 7,850 necropsies (1.4 per cent), and Kelynack [9] found 18 in 1,446 cadavers (1.2 per cent). Mitchell [10] found 39 in 1,635 necropsies (2.4 per cent); Harkins [11] reported 41 in 2,400 necropsies (1.7 per cent). The incidence of Meckel's diverticulum in these investigations is 1.3 per cent.

The diverticulum exists because of failure of the vitelline duct to become obliterated. This process of closure usually occurs at the seventh week of embryonic development. Failure of the complete process of atrophy of the ducts results in Meckel's diverticulum, or umbilical anus. Many have been found in postmortem examinations that had never given symptoms. Complications of Meckel's diverticulum are few. It has been estimated that about 15 to 20 per cent of all the diverticula are diagnosed (Faust [12]). Christie [13] in studies on infants found that complications were present in 15.8 per cent of cases. The chief complications were inflammation and peritonitis. Faust [12] stated that in a twenty-one year period at the Mayo Clinic Meckel's diverticulum was encountered 135 times. In about 30 per cent of cases it was definitely diseased and was of clinical significance. Some estimate of its infrequency as a source of symptoms in the diseases of childhood is obtained from the experience of Mixter. [14] He stated that while 32 patients were operated on for Meckel's diverticulum, 1,815 appendectomies and 2,674 herniorrhaphies were done in the same period.

When a pathologic process does exist in this structure, however, the most common findings are: (1) diverticulitis; (2) hemorrhage; (3) intestinal obstruction, and (4) incarceration in an umbilical or inguinal hernia or (rarely) in a femoral hernia.

Femoral hernia also occurs rather commonly. This type of hernia is not nearly as common as inguinal hernia, but it frequently occurs in association with the latter and passes unrecognized unless the region is carefully examined. Andrews [15] drew attention to the fact that many

7. Turner, cited by Doolin, W.: Acute Abdominal Emergencies Due to the Presence of Meckel's Diverticulum, Irish J. M. Sc. **43**:299-305, 1929.

8. Forque, E., and Riche, V.: Le diverticulae de Meckel, Paris, Octave Doin, 1907.

9. Kelynack, T. N.: On Meckel's Diverticulum, Brit. M. J. **2**:459-466, 1897.

10. Mitchell, L. J.: Notes on a Series of Thirty-Nine Cases of Meckel's Diverticulum, J. Anat. & Physiol. **32**:675-678, 1898.

11. Harkins, H. N.: Intussusception Due to Invaginated Meckel's Diverticulum, Ann. Surg. **98**:1070-1095, 1933.

12. Faust, L. S.: Meckel's Diverticulum with Unusual Clinical Manifestations, M. Clin. North America **15**:1483-1489, 1932.

13. Christie, A.: Meckel's Diverticulum: A Pathologic Study of Sixty-Three Cases, Am. J Dis. Child. **42**:544 (Sept.) 1931.

14. Mixter, C. G.: Meckel's Diverticulum and Its Surgical Significance, Proc. Inst Med. Chicago **9**:286-308, 1933.

15. Andrews, E. W.: Personal communication to the authors.

recurrences of inguinal hernia are wrongly diagnosed and are preexisting femoral hernias which were overlooked by the surgeon at the time of the surgical repair. The incidental ratio of femoral hernia to inguinal hernia is about 1 : 25 (Watson [16]).

Protrusion of Meckel's diverticulum through a hernial opening is not a great rarity. In 1924, Watson [16] was able to collect 147 cases from the literature. The vast majority of such hernias occur in the inguinal region. Ninety-six of this series accompanied inguinal hernias, and 34 accompanied femoral hernias. It is, therefore, unusual to observe the combination of a femoral hernia and Meckel's diverticulum. A review of the literature since 1700 reveals 16 cases of Meckel's diverticulum incarcerated in femoral hernia (Sweet [17]). Fourteen were reported prior to Jan. 1, 1929, and Sweet [17] and Donati [18] have each added 1 case since that time. Two cases of Meckel's diverticulum incarcerated in a femoral hernia have been observed at St. Luke's Hospital since 1933. We shall briefly review the records of these 2 cases.

REPORT OF CASES

CASE 1 (Dr. McArthur).—A woman aged 72 entered St. Luke's Hospital with a history of nausea of sixteen hours' duration and of swelling in the right inguinal region of twenty-two hours' duration. The patient had known of a swelling the size of an English walnut in the right inguinal region for five years. In walking about the house she slipped, falling to the floor. At that time she felt a snap in the right inguinal region and noticed that the swelling had increased to the size of a hen's egg. About six hours later she became nauseated and vomited small quantities on three or four occasions. At no time was there pain in the region of the swelling.

Physical examination on admission to the hospital revealed a temperature of 99.6 F. and a pulse rate of 68. The blood pressure in millimeters of mercury was 168 systolic and 80 diastolic. The erythrocytes numbered 3,600,000 and the leukocytes 16,000 per cubic millimeter of blood. The value for hemoglobin was 14.23 Gm. per hundred cubic centimeters of blood. The differential blood count was normal, and examination of the urine gave negative results.

With the patient under ethylene anesthesia an oblique inguinal incision was made. The mass encountered was a portion of small bowel tightly covered with omentum. When the strangulated bowel was released the color quickly returned to normal, and the bowel was replaced in the abdomen. The hernial opening was closed with interrupted chromic catgut sutures. The postoperative course was uneventful for thirty-six hours, after which time the patient began vomiting small quantities of small bowel contents. A nasal tube was placed into the stomach and suction applied. One thousand and ninety cubic centimeters of small bowel contents was recovered in three hours. A secondary operation was performed forty hours after the first.

16. Watson, L. F.: Hernia, St. Louis, C. V. Mosby Company, 1924, p. 660.

17. Sweet, R. H.: Incarceration of a Meckel's Diverticulum: Review of the Literature, New England J. Med. **202**:997-998, 1930.

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ROLE OF THE RESPIRATORY TRACT IN CONTAMINATION OF AIR

A COMPARATIVE STUDY

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AND

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In a previous publication by one of us (D. H.) [1] it was noted that the number of staphylococci in the air of an operating room varies directly with the number of occupants. On several occasions throughout the year cultures of material from the noses and throats of the operating room personnel were made, and it was found that contamination of the air with Staphylococcus aureus varied directly with the number of carriers of this organism and the density of the growth in the naso-pharynx. A group selected at random from the general population on one occasion showed about the same percentage of carriers as had been found among the personnel of the operating room. During the winter of this year (1933-1934) the number of carriers at times ran as high as 80 per cent.

During the past year, sediment from the air of the operating room has been cultured weekly (chart 1). The number of colonies of Staph. aureus haemolyticus as well as the total number of colonies of all organisms per Petri dish was much lower than during the winter of 1933-1934, when our first cultures were made.[1] During the past year the average number of carriers of Staph. aureus in the nose and throat was not above 15 per cent, as compared with a maximum of 80 per cent when the higher degree of contamination of air was present (in 1934).

We have determined repeatedly by cultures that when occupancy is terminated the air becomes progressively more free of sedimenting viable bacteria even when electric fans are used to agitate the air. The rapidity with which the air becomes free of these sedimenting bacteria is illus-trated by chart 2. Although in this chart we have no accurate record of the length of time the room had been vacant, in general it was occupied
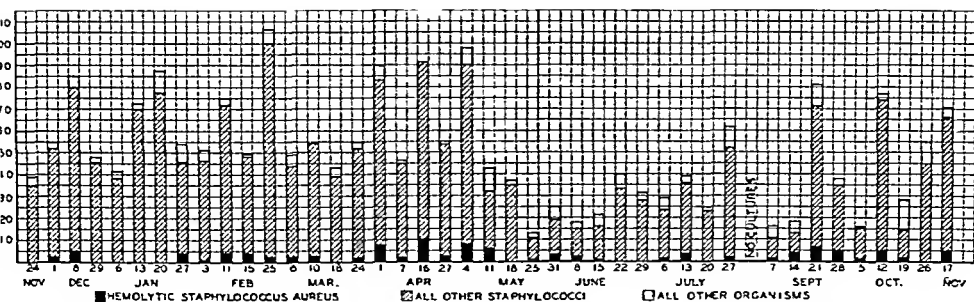
Chart 1.—Weekly cultures of sediment from the air of an operating room during occupancy, showing the prevalence of staphylococci and other organisms settling on a Petri dish of blood agar during an exposure of one hour. All plates were incubated for forty-eight hours at a temperature of 37.5 C. The colonies were then identified and recorded. Organisms other than staphylococci were few, were all relatively nonpathogenic and in this chart are grouped together for simplicity. Note the fluctuations in the number of organisms, particularly the great reduction during the warmer months. Staph. aureus haemolyticus appeared frequently but in relatively small numbers. At times this organism may be more numerous; it has caused the majority of the operating room infections coming under our observation. Such infections in clean primary incisions have been all but eliminated by sterilization of the air in the operating room.[5b]
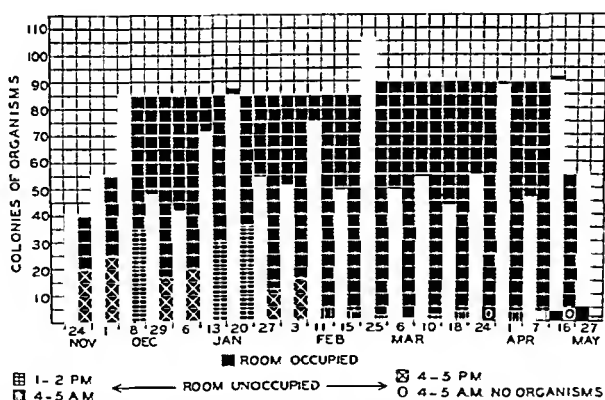
Chart 2.—Weekly cultures of sediment from the air in an operating room. showing the rapid reduction in the number of organisms settling from the air with cessation of occupancy. Each culture was made by exposure of a Petri dish of blood agar for one hour. This was incubated for forty-eight hours, and the colonies were then identified and recorded. This chart shows only the total number of organisms. In both the occupied and the unoccupied room the proportions were approximately the same as are shown in chart 1.

While the time since occupancy cannot be accurately given each week, in general the room was occupied until near noon and was not used during the afternoon or night when these cultures were made. No culture was made immediately after termination of occupancy.

until about noon, was not used during the afternoon or night when cultures were to be made and was never tested immediately after occupancy was terminated. It has been observed that with resumption of occupancy there is rapid recontamination of the air. When adjacent rooms and corridors are occupied there is a slight to moderate rise in contamination in a closed, unoccupied operating room, indicating some transmission of organisms by air currents through cracks under and around doors or through openings that cannot be closed tightly.

Before we began sterilization of the air in the operating room it was our policy for a number of years to postpone extensive operative procedures, such as thoracoplasties, until the summer, in order to avoid the greater risk of infection during the periods of greatest contamination of air. At all times such important operative procedures were performed in the morning in a room which had been unoccupied for at least twelve hours and which contained as few occupants as possible during the operation. We felt that the greatest source of pollution of the air was the nose and throat and not the skin or the incoming air, though both of these may at times be of some significance. This opinion was based on our cultural studies showing the relation between the presence of Staph. aureus in the noses and throats of the operating room personnel and the degree of contamination of air [1] and on the published reports showing the relation between the presence of streptococci in the nasopharynxes of the operating room personnel and the prevalence of wound infections caused by this organism.[2]

In order to determine more accurately the relation between the flora of the nose and throat and contamination of the air, it was decided to make a comparative study extending over a year. Ten men who spent most of each day in one room were selected. At weekly intervals during the last hour of the day's occupancy a Petri dish of blood agar was exposed to sedimentation from the air. During and at the end of this time material from the nose and throat of each occupant was cultured as follows:

The mucous membranes were swabbed with an ordinary cotton applicator. This was washed in 10 cc. of broth. The resultant suspension was diluted 1:100, and 0.1 cc. of this dilution was added to 10 cc. of agar and 2 cc. of blood and poured as a plate. All cultures were incubated for forty-eight hours at 37.5 C. The colonies were then identified and recorded.

2. (a) Meleney, F. L.: Seasonal Incidence of Hemolytic Streptococcus in the Nose and Throat, in Surgical Operating Personnel: Significance of Masking During Operation, J. A. M. A. 88:1392-1394 (April 30) 1927. (b) Meleney, F. L., and Stevens, F. A.: Postoperative Haemolytic Streptococcus Wound Infections and Their Relation to Haemolytic Streptococcus Carriers Among the Operating Personnel, Surg., Gynec. & Obst. 43:338-342 (Sept.) 1926. (c) Meleney, F. L.: Infection in Clean Operative Wounds: A Nine Year Study, ibid. 60:264-276 (Feb. 15) 1935. (d) Walker, I. J.: How Can We Determine the Efficiency of the Surgical Mask? ibid. 50:266-270 (Jan., no. 1A) 1930.

In making the cultures of material from the air, sedimentation was used rather than the air centrifuge method of Wells,[3] since it was felt that this would give a more accurate estimate of the number of organisms which might settle on the sterile supplies and on the open wound.

Certain difficulties were encountered. such as the fact that Streptococcus viridans alpha is not found viable as a surface colony on the blood agar plate exposed in the room. although it may be obtained by other methods. Staphylococcus albus was the organism most frequently cultured on the open plate, while Str. viridans alpha was most commonly found in the nose and throat. The relative rise and fall of the level of contamination by Str. viridans alpha shown in the cultures of material from the throat was, however, fairly well paralleled not only by the rise and fall of the level of contamination by Staph. albus in the nose and throat but also by the number of colonies of Staph. albus
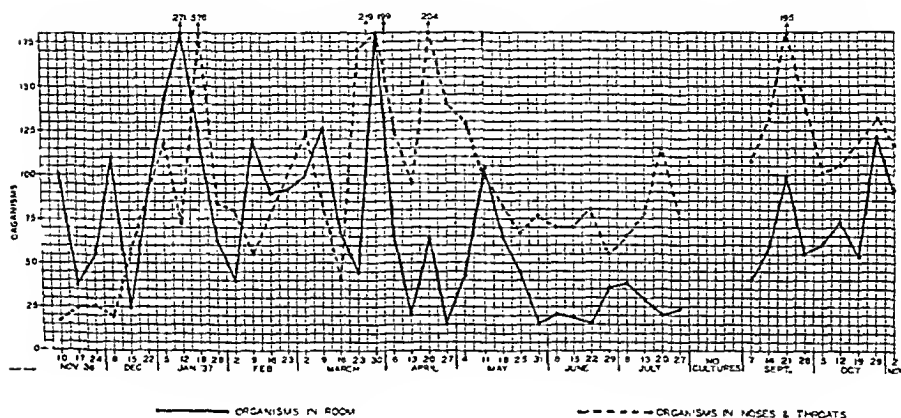
Chart 3.—Weekly cultures showing the relation between the number of organisms in the air of an occupied room and the degree of contamination of the noses and throats of the occupants. Our records show the total number of colonies of each organism (see chart 4 for Staph. aureus haemolyticus), but the proportions were approximately the same as those given in chart 1, and the curves were roughly parallel; to preserve the simplicity of the chart, therefore, only the totals are given. The low degree of contamination of the air and the high degree of contamination of the nasopharynx during April are explained by a drop in the number of organisms in the nose and throat except for Str. viridans alpha. which continued to be present in large numbers and which is not recovered from the air as a surface colony on blood agar.

sedimenting from the air. (For exception see chart 3.) In general the number of colonies of staphylococci (which are easily cultured on an open plate) can be taken as an index of the degree of contamination of

3. Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. **107**: 1698-1703 (Nov. 21) 1936; Air-Borne Infection: Sanitary Control, ibid. **107**:1805-1809 (Nov. 28) 1936.

air. The total number of all organisms cultured from the air of the room roughly parallels the total number cultured from the noses and throats of the occupants (chart 3).

Chart 4 indicates the days on which Staph. aureus haemolyticus appeared in the cultures of material from the air or the nasopharynx or both and the comparative number of organisms present in each place. This organism was grown from the nasopharynx or from the air of the room or both on twenty-two occasions during the making of the cultures. On 16, or 73 per cent, of these occasions they were present in both places at the same time. In 3 cultures they were obtained from the nose and throat and not from the air of the room, and on three occasions they were found in the air but not in the nose and throat.
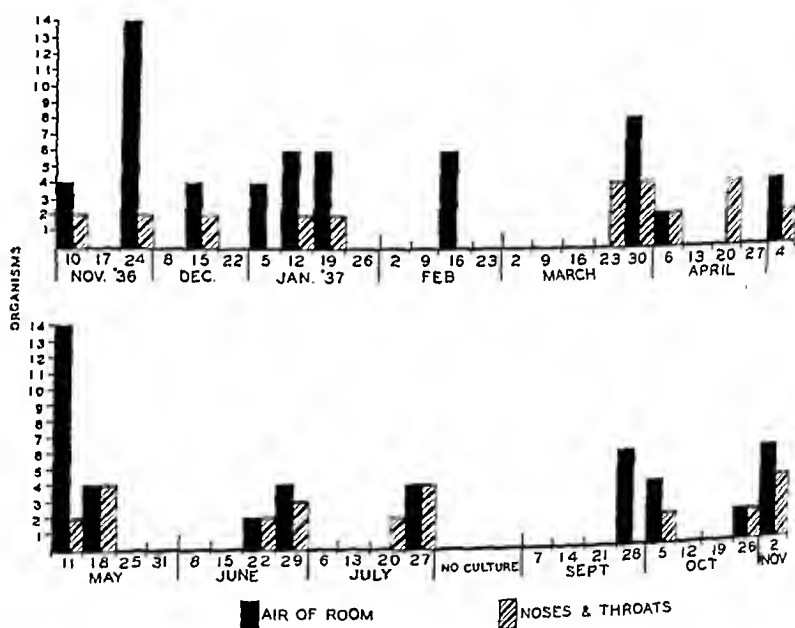
Chart 4.—Weekly cultures showing the correlation between the prevalence of Staph. aureus haemolyticus in the air of an occupied room and its presence in the noses and throats of the occupants. Forty-five cultures were made at weekly intervals, with the following results: Cultures of sediment from the air and cultures of material from the nasopharynx were similar in 87 per cent of instances. Staph. aureus haemolyticus was present in both in 36 per cent and absent in both in 51 per cent of instances; this organism was present in the nasopharynx and absent in the air in 6.5 per cent and was present in the air and absent in the nasopharynx in 6.5 per cent. Ruling out the positive cultures of sediment from the air or material from the nasopharynx which occurred alone but immediately preceding or following a week in which cultures both of sediment from the air and of material from the nose and throat yielded bacteria, there were only one isolated culture of sediment from the air (Feb. 16) and one isolated culture of material from the nose and throat (April 20) which yielded bacteria, or only 4 per cent of the total number of weekly cultures made.

On only two occasions, however, were they found singly except during the week immediately preceding or following a week when they were

cultured both from the air and from the nose and throat. As has been shown by Meleney and his colleagues [4] and by Walker [2d] from cultures of streptococci and by this and the previous report by one of us (D. H.)[1] for staphylococci, there is generally a low level of contamination by organisms in the air and in the nose and the throat during the summer.

It seems apparent from these cultures that there is a definite correlation as to both the type and the number of organisms found in the air of a given room and in the noses and throats of a group of regular occupants of that room. The question has been raised whether the noses and throats are contaminated by the organisms floating in the air in the room rather than that the air becomes contaminated by organisms from the nose and throat. Unquestionably infections may be, and probably most infections of the respiratory tract are, transmitted by this route. On the other hand, it seems most likely that the pathogenic bacteria found in the air have been given off from the noses and throats of carriers. As is shown in chart 2 and as has been repeatedly observed on other occasions, a Petri dish (with a surface measuring 63.4 sq. cm. [9.83 square inches]) of blood agar exposed to sedimentation for one hour in a room that has been closed and free of occupants for twelve hours or longer will show, on incubation, results varying from no growth up to four or five colonies of organisms, most commonly Staph. albus or Proteus vulgaris. The count is always low, even if the air and dust are agitated by electric fans, but it rises rapidly as soon as the room is occupied. From this it would seem that organisms die out rather than multiply in a room that has become contaminated and that bacteria must be brought in by the occupants. Material from shoes, hair, clothing, walls and the dust of the room has been cultured, but relatively few organisms have been found. Staph. albus in large numbers may be cultured from material from the skin, but the number and type of colonies cultured from material taken from the nose and throat seem to parallel more nearly the number and type of colonies cultured from sediment from the air. It also seems more logical that organisms should be expelled by the air currents from the respiratory passages than that they should come off the skin, which frequently is moist and usually is covered by a gown.

This work, undertaken to study the bacterial flora floating in the air of an occupied room and to compare this with the organisms found in the noses and throats of its occupants, has shown other interesting data. At certain times Str. viridans was found in tremendous numbers in cultures of material from the nose and throat. During such periods the bacteriologic laboratory reported that all cultures of pharyngeal material, from resident as well as from ambulatory patients, showed

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4. Meleney.[2a,c] Meleney and Stevens.[2b]

a similar high level of contamination with this organism. Coincidentally, several of the experimental personnel had infections of the upper part of the respiratory tract, and the number of patients admitted to the hospital with such infections was large.

Comparison of data on the weather with the charted number of organisms showed a definite increase in contamination of the nose, the throat and the air after several days of rain. Conversely, after a period of bright, clear weather (regardless of temperature) the level of contamination in the nasopharynx and in the air was lower.

During the several years that we have more or less regularly cultured sediment from the air of the operating room and occasionally cultured material from the noses and throats of the personnel, as well as in the weekly cultures reported in this paper, Streptococcus haemolyticus beta has only rarely been found in the cultures of material from the throat. Reports in the literature lead us to believe that this organism may be more prevalent in certain other parts of the United States.[2d] During this time we have had virtual freedom from streptococcic wound infections. On the contrary, Staph. aureus haemolyticus has been the most virulent and the most frequent pathogenic organism found by us in the nasopharynx and in the air (charts 1 and 4) and has caused over 90 per cent of infections in supposedly clean operative wounds coming under our observation. With us this reached its peak in 1933-1934. The widespread distribution of this organism and the number and severity of the wound infections caused by it forced us to try various measures for its control. Bactericidal irradiation to sterilize the contaminated air has been the most effective of these, giving satisfactory results when all other measures have failed, at least partly.[5] In another hospital, located in the notheastern portion of the United States, where cultures showed Staph. aureus to be present in the air in large numbers,[6] there were 3 wound infections with this organism during the three week period during which cultures were made. The widespread distribution of this organism in the air of the operating rooms has been

5. (a) Hart, D.: Sterilization of the Air in the Operating Room with Bactericidal Radiation: A Comparative Analysis of One Hundred and Thirty-Two Individual Stages of Extrapleural Thoracoplasties Performed with Radiation and One Hundred and Ten Stages Performed Without Radiation, J. Thoracic Surg. 7:525-535 (June) 1938; (b) Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy: Results in Over Eight Hundred Operations, Arch. Surg. 37:956 (Dec.) 1938. (c) Hart, D., and Sanger, P. W.: Effect on Wound Healing of Bactericidal Ultraviolet Radiation from a Special Unit: Experimental Study, ibid., to be published. (d) Hart, D.; Devine, J. W., and Martin, D. W.: Bactericidal and Fungicidal Effect of a Special Ultraviolet Radiation Unit Used for Sterilizing the Air in the Operating Room, ibid., to be published.

previously reported.[6] Should Str. haemolyticus beta become a common contaminant of the nasopharynx in this or any section we should expect an increase in the number of wound infections with this organism. A report by Walker [2d] from a teaching hospital in Boston demonstrates this clearly. With a rise in the number of carriers of Str. haemolyticus beta to between 25 and 50 per cent the incidence of streptococcic wound infections rose from a base line of zero during May, June, July and August to 10.5 per cent during March. At the same time the total number of infections rose from a base line of 8 per cent (average) during May through August to 42 per cent during March. In the same article, Walker reported that in sixteen hospitals in which seasonal epidemics of wound infections were said to have occurred the average rise was from a base level of 1.25 per cent during May through August to a peak of 8 per cent during March. It seems certain both from our experience and from the reports in the literature that in different places and at different times in the same place there are wide variations in the type of organism in the nose and throat and in the intensity of its growth. This is well illustrated by the widespread distribution of streptococci during the epidemic of influenza in 1918, at which time in certain places it was necessary to close the operating rooms for all except emergency operations. It seems that infections in clean operative wounds roughly follow this curve of incidence contamination of the respiratory tract. Many physicians are familiar with instances of operating room infections caused by the same organism which have reached almost epidemic proportions. In many instances these organisms must come from the nasopharyngeal passages of the personnel. We are convinced that in the majority of cases of so-called unexplained operating room infections, even when the conventional gauze mask is worn over both the mouth and the nose of every occupant, organisms from the respiratory tract are the cause of the infection and reach the wound and sterile supplies by way of the air rather than by contact.

SUMMARY

1. Staphylococci can be cultured readily from the air of an occupied room and furnish a fair index of the degree of contamination of the air.

2. The bacterial flora sedimenting from the air of a given room and that cultured from the mucous membranes of the noses and throats of the occupants of the room show a close similarity both as to number and as to type of organisms.

6. Hart, D.: Pathogenic Bacteria in the Air of Operating Rooms: Their Widespread Distribution and the Methods of Control, Arch. Surg. **37**:521-530 (Oct.) 1938.

3. When nasopharyngeal contamination in the experimental group is at a high level the same condition is found to exist in patients, students and other groups of persons.

4. With occupancy of a room there is a rapid rise in the number of viable bacteria floating in the air, the number and type of bacteria being dependent on the number of occupants and the intensity of the growth in their noses and throats.

5. With termination of occupancy there is a moderately rapid diminution in the number of viable organisms sedimenting from the air, so that in from twelve to twenty-four hours the number is negligible.

6. There is a definite seasonal variation in contamination of the nose, the throat and the air by both pathogenic and nonpathogenic organisms, the level of such contamination being lower in clear, dry weather than when it is wet and cloudy. The lowest contamination over a relatively prolonged period occurs during the warmer months.

CONCLUSIONS

In the modern operating room the noses and throats of the occupants are the chief source of contamination of the air and the operative wound, despite the use of the conventional gauze mask worn over the nose and mouth. Organisms reach the wound and sterile supplies predominantly by way of the air, since transfer of organisms by direct contact has been largely eliminated by so-called aseptic surgical technic. Until contamination of the air with pathogenic bacteria can be prevented it seems imperative that the air in the operating room should be sterilized. Bactericidal irradiation offers a practical method of accomplishing this.

EFFECT ON WOUND HEALING OF BACTERICIDAL ULTRAVIOLET RADIATION FROM A SPECIAL* UNIT

EXPERIMENTAL STUDY

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DURHAM, N. C.

AND

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CHARLOTTE, N. C.

Before utilizing a special ultraviolet irradiation unit for sterilizing the air in the operative region, with resultant exposure of the open wound, it seemed desirable to test the effect of radiation on wound healing in experimental animals.

As has been previously reported,[1] this unit consists of eight tubes 30 inches (75 cm.) long, mounted with two parallel tubes occupying the central part of each side of a square 5 feet (150 cm.) to the side. This square was mounted in a horizontal plane with its center approximately 4 feet 6 inches (137 cm.) above the operative site so as to place the center of each of the tubes about 5 feet from the incision. Over 80 per cent of the output of these radiation tubes is at 2,537 angstrom units. The intensity of radiation at the operative site, as measured by a photoelectric cell sensitive to this wavelength and calibrated with a bismuth-silver vacuum thermopile, is 28 to 30 microwatts per square centimeter.[2] A blond person exposed at this point for eighty minutes received no appreciable burn. There were some redness of the skin and a prickly sensation, which cleared within twenty-four hours. It has been demonstrated that with this intensity of radiation

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* Ultraviolet irradiation unit with over 80 per cent of its output at 2,537 angstrom units, giving an intensity of approximately 30 microwatts per square centimeter at the operative site.

1. Hart, D.: Operation Room Infections: Preliminary Report, Arch. Surg. 34:874-896 (May) 1937.

2. Sharp, D. G.: A Quantitative Method of Determining the Lethal Effect of Ultraviolet Light on Bacteria Suspended in Air, J. Bact. 35:589-599 (June) 1938.

and with exposure of less than five minutes the percentage of sterilization of a Petri dish of blood agar inoculated with Staphylococcus aureus haemolyticus [1] and other organisms [3] is between 95 and 100. It has also been shown that at this point this intensity of radiation reduces by over 95 per cent [1] the number of viable organisms dropping from the air.

MATERIAL AND METHOD

White rats were used for the shorter and dogs for the longer experiments. All operations were performed with the animals under ether anesthesia, and aseptic surgical technic was scrupulously followed except that in no case was any attempt made to keep sterile dressings in place after the operation. The incisions in rats for the first four groups of experiments were uniformly 3 to 4 cm. in length; those in dogs were made 12 to 15 cm. long, in order to allow greater exposure of the peritoneal surface. Closure was made in layers with interrupted sutures of black silk. The same technic was used for the control wounds except that they were exposed to the air with the same conditions under which the others were exposed to bactericidal radiation.

The following types of experiments were carried out:

1. Wounds were made in the abdominal wall down to the peritoneum and exposed as follows: in 3 rats, to bactericidal radiation for ten minutes; in 3 rats, to bactericidal radiation for twenty minutes; in 3 rats to bactericidal radiation for thirty minutes; and in 3 rats (controls), to air for ten, twenty and thirty minutes, respectively.

The animals were observed for three days after the operation.

2. Four incisions were made down to the peritoneum in the abdominal wall of each of 6 rats. One incision on each animal was used as a control, and the others were exposed for ten, twenty and thirty minutes respectively. A lead plate was used to protect the unexposed portion of each animal as well as the control wound. This group was observed for five days after the operation (fig. 1).

3. Incisions, one to either side of the midline, were made deep into the muscles of the back in each of 4 rats. Two wounds were exposed for ten minutes, two for twenty minutes and two for thirty minutes. Two were used as controls. This group was observed for five days after operation.

4. Bilateral incisions were made deep into the muscles on the posterior surfaces of the hindlegs of 8 rats. For each rat one incision was exposed to radiation and the other to the air for thirty minutes, the animal and the wound exposed to the air being protected from the radiation by a lead plate. This group was observed for six days.

After operation all wounds were observed for evidence of gross infection during periods varying from three to six days, as has been indicated. On the last day of observation the animals were killed, the wounds were grossly inspected, and blocks of tissue extending across the wound were taken for microscopic sections. From gross observation they were classified into four groups as follows:

    A. Healing by first intention
    B. Slight reaction
    C. Moderate reaction
    D. Gross suppuration

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3. Hart, D.; Devine, J. W., and Martin, D. W.: Bactericidal and Fungicidal Effect of Ultraviolet Radiation: Use of a Special Unit for Sterilizing the Air in the Operating Room, Arch. Surg., this issue, p. 806.

Fig. 1.—Comparison of the reaction in a wound (*A*) exposed to bactericidal radiation for thirty minutes with that in another wound (*B*) in the same animal, exposed to air for thirty minutes. Microscopic sections taken on the fifth day after exposure extend across the incision. From the study of a large number of sections it was our impression that there was less reaction in the wounds exposed to radiation. Certainly the reaction was no greater, and this is the point we wished to prove. It should be noted that in this case the control incision received some protection from the radiation, since it was in a room in which the air was being sterilized but was protected from the radiation by a sterile lead plate.

In all cases the microscopic observations as to the stage of healing and the wound reaction were classified into four groups, as follows:

A. Advanced primary healing

B. Primary healing in progress

C. Healing in progress but with some granulation tissue and inflammatory reaction

D. Slight healing with extensive inflammation

TABLE 1.—*Gross Appearance of Wounds*

Group*	Exposed to Bactericidal Radiation		Exposed to Air	
	Number of Wounds	Percentage of Irradiated Wounds in Each Group	Number of Wounds	Percentage of Control Wounds in Each Group
A	25	61.0	5	26.3
B	13	31.5	12	63.2
C	2	5.0	2	10.5
D	0	0	0	0
Died first day	1	2.5	0	0
Total	41	100.0	19	100.0

* In this table, groups A, B, C and D represent wounds classified as showing the following results: A, healing by first intention; B, slight reaction; C, moderate reaction; D, gross suppuration.

TABLE 2.—*Microscopic Study of Wounds*

Group*	Exposed to Bactericidal Radiation		Exposed to Air	
	Number of Wounds	Percentage	Number of Wounds	Percentage
A	19	46.4	4	21.0
B	15	36.6	13	68.4
C	5	12.2	1	5.3
D	1	2.4	1	5.3
Died first day	1	2.4	0	0
Total	41	100.0	19	100.0

* In this table, groups A, B, C and D represent wounds classified as showing the following results: A, advanced primary healing; B, primary healing in progress; C, healing in progress but with some granulation tissue and inflammatory reaction, and D, slight healing with extensive inflammation.

Since the four types of experiments were all similar and wound healing was about the same, the gross findings are tabulated in table 1, and the results of microscopic studies are recorded in table 2.

5. In order to test the effect of radiation on the peritoneum a long midline incision was made in each of 8 rats. In 6 the stomach, spleen and intestines were exposed to bactericidal radiation for thirty minutes. In the other 2 the same organs were exposed to the air for a similar period to serve as controls. The animals were killed seven days after the operation. There was no detectable difference in the number of adhesions, the amount of fluid or the appearance of the peritoneum.

6. In order to expose the peritoneum for a longer period than that during which a rat can be kept under anesthesia and to observe healing in the presence of soiling from an anastomosis in the gastrointestinal tract, 8 operations were carried out on 4 dogs. The results are shown in table 3, in which the gross appearance of the wound and of the peritoneal cavity are recorded. There was no evident difference in the amount of edema, the number of adhesions or the quantity of peritoneal fluid in the irradiated animals as compared with the

TABLE 3.—*Healing of Peritoneal Wounds in Dogs in the Presence of Anastomosis in the Gastrointestinal Tract*

Experiment	Dog	Operation	Peritoneum Exposed	Gross Appearance of Wound	Condition of Peritoneal Cavity Eight Days After Operation
1	T 1	Gastro-enterostomy	75 minutes	Silght reaction	Minimal adhesions around functioning gastroenterostomy
2	T 2	Gastro-enterostomy	80 minutes	Slight reaction	Minimal adhesions around functioning gastroenterostomy
3	T 3	Gastro-enterostomy	90 minutes	Healing by first intention	Few adhesions around functioning gastroenterostomy
4	T 4 Control	Gastro-enterostomy	Abdominal cavity left open without irradiation 80 minutes	Slight reaction	Minimal adhesions around functioning gastroenterostomy
5	T 1	Anastomosis of sigmoid (end to end) on 8th day after gastro-enterostomy had been done	90 minutes (week before, 75 minutes)	Wound broken down; fecal fistula	Fecal fistula; surprisingly few adhesions considering the pathologic picture
6	T 2	Same as experiment 5	80 minutes (week before, 80 minutes)	Healing by first intention	Relatively no adhesions or reaction
7	T 3	Same as experiment 5	90 minutes (week before, 90 minutes)	Healing by first intention	Relatively no adhesions or reaction
8	T 4 Control	Same as experiment 5	Abdominal cavity exposed to air without irradiation 90 min. (week before, 80 min.)	Slight reaction about wound	Essentially no difference from irradiated cavities

controls (fig. 2). In 1 case, after an end to end anastomosis of the colon, a fecal fistula developed. It was the opinion of the operator that irradiation was not responsible for the complication, and in this case there were remarkably few adhesions considering the leakage of intestinal contents.

7. In a number of dogs the brain or the spinal cord was exposed to radiation for sixty minutes, and in control animals these structures received a similar exposure to air. When the brain was exposed either to the air or to radiation there was no evident neurologic disturbance. When the spinal cord was exposed either to radiation or to air, certain dogs showed some weakness of the hindlegs, either as a result of poor surgical technic or owing to impairment of the stability

of the spinal column by the extent of the laminectomy. This weakness was thought to be related to the operative procedure rather than to the irradiation, since it affected the control dogs as well as the dogs exposed to radiation.

On both gross and microscopic examination of the brain (fig. 3) and the spinal cord (fig. 4) there was no demonstrable difference between the irradiated brain or spinal cord and the control. Further tests are being carried out on
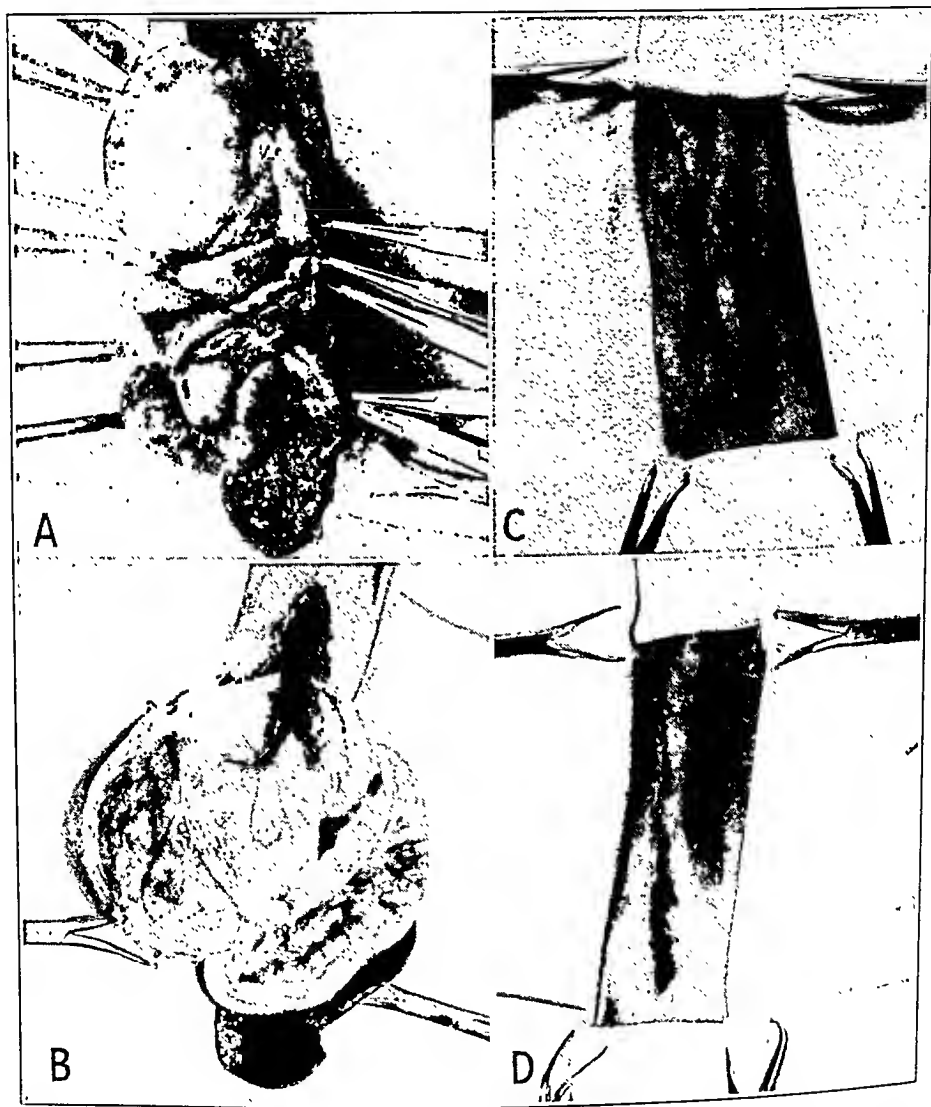
Fig. 2.—*A*, peritoneum (dog T2, table 3) exposed to radiation for eighty minutes. Gastroenterostomy was performed without the usual coverings of warm, moist pads. *B*, peritoneum (dog T4, table 3) exposed to air for eighty minutes as a control. Gastroenterostomy was performed without the usual coverings of warm, moist pads. In both the experimental and the control animal there was a notable absence of adhesions or other peritoneal reaction. *C*, abdominal incision (dog T2, table 3) exposed to bactericidal radiation for eighty minutes in addition to the time required for opening and closing. *D*, abdominal incision (dog T4, table 3) exposed to air for the same period, as a control. Healing of the abdominal incision was better in the animal exposed to radiation than in the control, although both are recorded as showing a slight reaction (table 3).

dogs by an investigator trained in neurosurgical technic, and the tissues are being studied by means of special stains.

Since these experiments were carried out, over 1,000 operations have been performed on patients, with no demonstrable ill effect on the skin, peritoneum, meninges or other tissue exposed in the wound.[4]
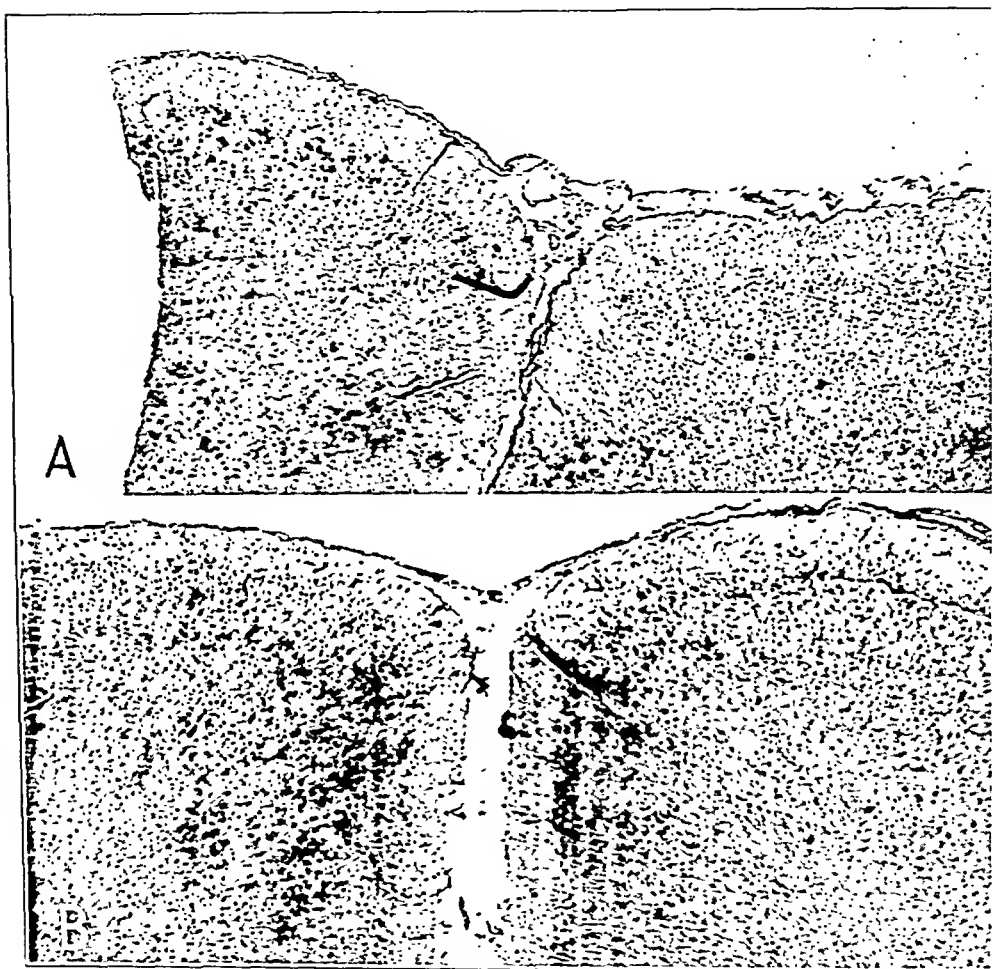
Fig. 3.—Photomicrographs of the brains of 2 dogs fourteen days after operation (hematoxylin and eosin stain). *A*, brain exposed to bactericidal radiation for sixty minutes. *B*, control specimen, exposed to air for sixty minutes. In both cases the brain was kept moist but was not otherwise protected. There was no appreciable difference between the irradiated brain and the control.

4. Hart, D.: Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy: Results in Over Eight Hundred Operations, Arch. Surg. **37:**

No attempt is made to protect the skin or the wound beyond the precautions included in our usual operating room technic. This consists in covering the skin as soon as the incision is made, in avoiding undue exposure of the viscera or other denuded tissue and in keeping the exposed brain or spinal cord covered with warm, wet cotton. We have
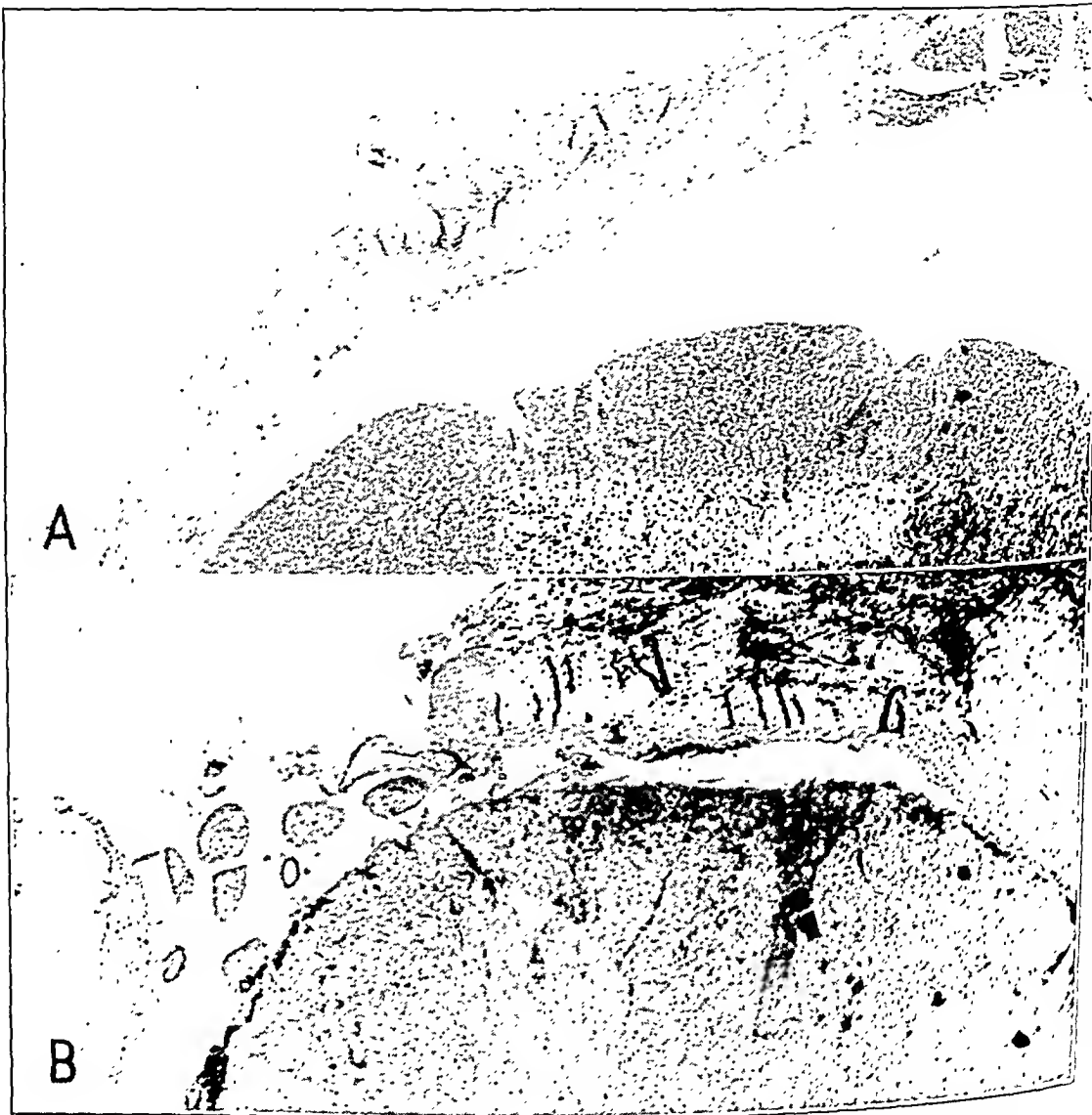
Fig. 4.—Photomicrographs of the spinal cords of 2 dogs fourteen days after operation (hematoxylin and eosin stain). A, spinal cord exposed to bactericidal radiation for sixty minutes. B, control specimen, exposed to air for sixty minutes. In both cases the spinal cord was kept moist but was not otherwise protected. There was no appreciable difference between the irradiated cord and the control.

956 (Dec.) 1938; Sterilization of the Air in the Operating Room with Bactericidal Radiation: Comparative Analysis of One Hundred and Thirty-Two Individual Stages of Extrapleural Thoracoplasties Performed With Radiation and One Hundred and Ten Stages Performed Without Radiation, J. Thoracic Surg. 7: 525-535 (June) 1938.

avoided exposing the spinal cord for more than twenty to thirty minutes. It is seldom necessary to expose any part of a wound for a longer period. In such operations as radical mastectomy and repair of a large ventral hernia the tissues have been exposed for much longer periods without evident damage.

SUMMARY

Wounds in animals exposed for from ten to ninety minutes to bactericidal radiation as it is used to sterilize the air in the operative field healed as well as control wounds, if not better.

Exposure of the peritoneum to this intensity of radiation for from thirty to ninety minutes produced no damage demonstrable by adhesions, edema or increased fluid in the cavity.

Subsequent operations on over 1,000 patients with the wound exposed to an intensity of radiation at least as great as this have caused no demonstrable harm to the skin, peritoneum, meninges or other tissues exposed. The wounds heal with less reaction and less risk of infection, and there is less systemic reaction.

CONCLUSIONS

Bactericidal irradiation, which will render the air in the operative region almost free of viable organisms, offers little, if any, risk of damage to the patient if his eyes are protected and the usual precautions are taken to avoid prolonged and unnecessary exposure.

Healing is better in an irradiated wound than in one not irradiated, there being less danger of infection and less local and systemic reaction.

The slight inconvenience of protecting the eyes and skin of the operating room personnel is overbalanced by the greater security given the patient, particularly for extensive operative procedures performed during those times of the year and in those operating rooms in which there are a considerable number of pathogenic bacteria in the air.[5]

5. Hart, D.: Pathogenic Bacteria in the Air of Operating Rooms: Their Widespread Distribution and the Methods of Control, Arch. Surg. **37**:521 (Oct.) 1938. Hart, D., and Schiebel, H. M.: Role of the Respiratory Tract in Contamination of Air: A Comparative Study, ibid. **38**:788 (April) 1939.

BACTERICIDAL AND FUNGICIDAL EFFECT OF ULTRAVIOLET RADIATION

USE OF A SPECIAL [*] UNIT FOR STERILIZING THE AIR IN THE OPERATING ROOM

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There are many reports in the literature dealing with the effect of ultraviolet radiation on bacteria. In an effort to kill the bacteria floating in the air of the occupied operating room we turned to such radiation, which is known to have strong bactericidal properties. (Wells [1] has been working on a similar problem, an attempt to control contamination of air from the standpoint of public health.) We have used cold tubes 30 inches (75 cm.) long, containing argon, neon and mercury. Over 80 per cent of the output of such tubes (which have already been described [2]) is at 2,537 angstrom units, and the apparatus offers the following advantages:

1. High output in the bactericidal range of the spectrum and low output in the erythemic range.

2. Negligible production of ozone, which is rarely detectable by odor even with as many as sixteen tubes burning in the operating room.

3. Negligible production of heat.

4. Low cost of the irradiation unit, which is made of high transmission glass instead of quartz.

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* Over 80 per cent of the output at 2,537 angstrom units, giving an intensity of approximately 30 microwatts per square centimeter at the point of exposure.

1 Wells, W. F., and Wells, M. W.: Air-Borne Infection, J. A. M. A. 107:1698-1703 (Nov. 21) 1936; Air-Borne Infection: Sanitary Control, ibid. 107: 1805-1809 (Nov. 28) 1936.

2. Sharp, D. G.: A Quantitative Method of Determining the Lethal Effect of Ultra-Violet Light on Bacteria Suspended in Air, J. Bact. 35:589-599 (June) 1938
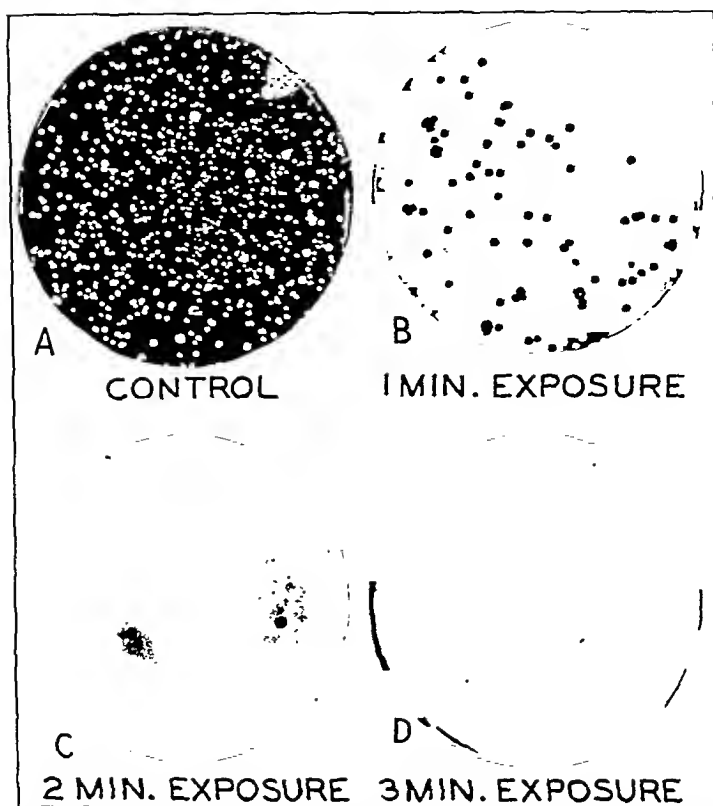
Fig. 1 (Staph. albus).—Photographs of one series of blood agar plates exposed to bactericidal radiation at a distance of 5 feet (150 cm.), from eight irradiation tubes each 30 inches (75 cm.) long. These tubes were arranged on a horizontal square 5 feet (150 cm.) to the side, with two parallel tubes occupying the central 30 inches (75 cm.) of each side. The center of the square was approximately 4.5 feet (135 cm.) above the Petri dish, so that the organisms were 5 feet (150 cm.) from the center of the individual tubes. Measurement of the intensity of the radiation at this point with a photoelectric cell sensitive to radiation at 2,537 angstrom units and calibrated with a bismuth-silver vacuum thermopile[2] showed it to be approximately 28 to 30 microwatts per square centimeter. Staph. albus is representative of organisms quickly killed by a given intensity of radiation. *A*, control plate sprayed with a dilute culture of Staph. albus; *B*, plate similarly prepared, photographed after irradiation for one minute; *C*, plate after irradiation for two minutes; *D*, plate after irradiation for three minutes. All plates were incubated for forty-eight hours at 37.5 C. before the colonies were counted and the photographs taken.

Staphylococcus citreus and Bacillus proteus showed about the same resistance (table 1).
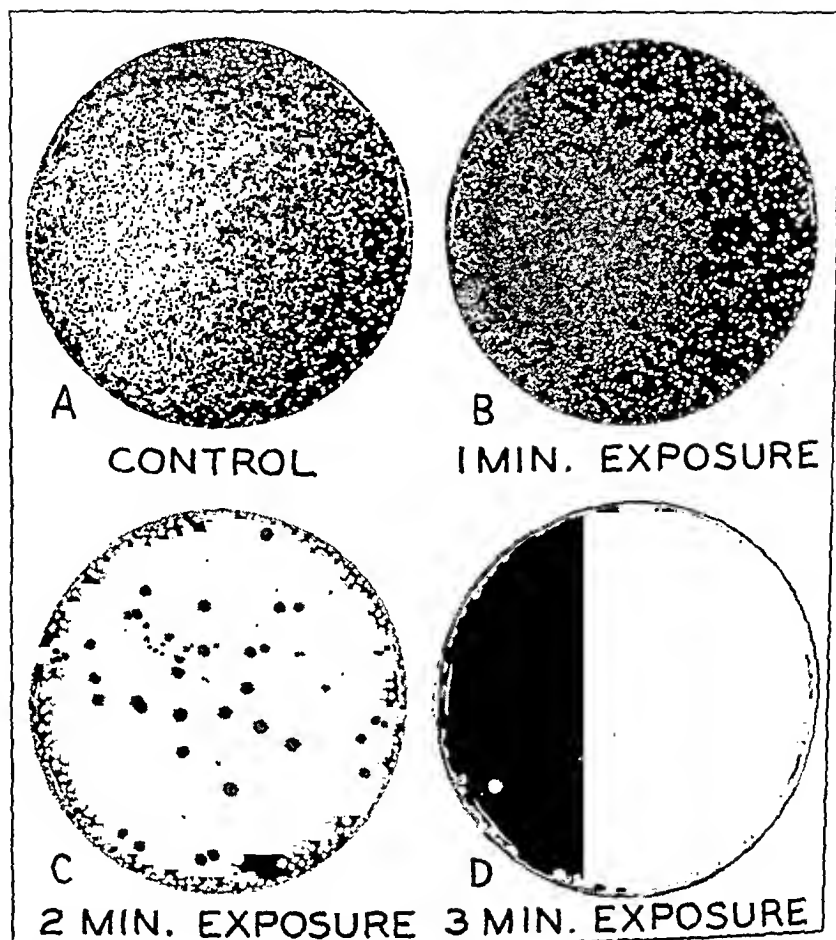
Fig. 2 (B. pyocyaneus).—Photographs of one series of blood agar plates exposed to bactericidal radiation under conditions identical with those given for figure 1. It should be noted that more colonies of this organism than of Staph. albus (fig. 1) survived a given period of exposure. This is probably accounted for partly by the increased density of the inoculation, but, in addition, B. pyocyaneus seemed to have a greater resistance. The organisms on the periphery of the plate were shaded from part of the radiation by the upright edge of the dish and survived longer than those not so shaded. *A,* control plate sprayed with a dilute culture of B. pyocyaneus; *B,* similarly treated plate after irradiation for one minute; *C,* plate after irradiation for two minutes; *D,* plate after irradiation for three minutes.

Bacillus coli and Streptococcus haemolyticus beta had about the same resistance (table 1).

5. Low operating cost (the estimated life of the tube is four thousand to five thousand hours, and from ten to sixteen tubes can be operated with as little current as is required by a 150 watt electric light bulb).

One of us (D. H.[3]) has already reported the effect on Staphylococcus aureus of radiation from eight such tubes at distances varying from 5 to 10 feet (150 to 300 cm.) and has shown its efficiency in reducing the number of viable bacteria floating in the air in the vicinity of the incision and sterile supplies. The widespread distribution of pathogenic bacteria in the air of the operating room has also been shown in a previous publication.[4]
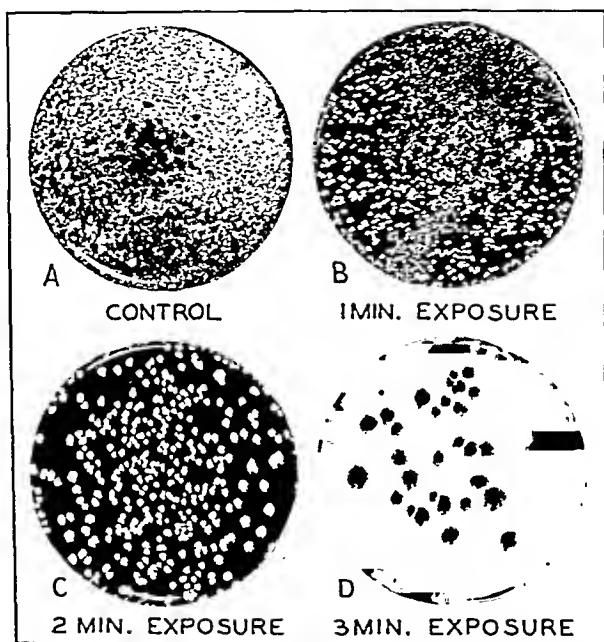
Fig. 3 (B. subtilis).—Photographs of one series of blood agar plates exposed as indicated for figure 1. This is representative of the most resistant of the bacteria tested. A similar picture was given by Friedländer's bacillus (Klebsiella pneumoniae, table 1). In contrast to the results shown in figures 1 and 2, a number of colonies in the central part of the plate, without any shading, survived an exposure of three minutes. The inoculation was fairly dense, and this probably played some part in the increased number of survivals. In addition, the resistance of the organism seemed to be greater. *A*, control plate sprayed with a dilute culture of B. subtilis; *B*, similarly prepared plate after irradiation for one minute; *C*, plate after irradiation for two minutes; *D*, plate after irradiation for three minutes.

3. Hart, D.: Operation Room Infections: Control of Air-Borne Pathogenic Organisms, with Particular Reference to the Use of Special Bactericidal Radiant Energy; Preliminary Report, Arch. Surg. **34**:874-896 (May) 1937.

4. Hart, D.: Pathogenic Bacteria in the Air of Operating Rooms: Their Widespread Distribution and Methods of Control, Arch. Surg. **37**:521 (Oct.) 1938.

This report makes no claim of discussing exhaustively the effect of ultraviolet radiation on bacteria. It is made to show the lethal effect produced with the particular irradiation unit used for this group of experiments on various bacteria and fungi at a distance of 5 feet (150 cm.) from each of the eight radiation tubes, that is, at the operative site as the tubes are mounted in the operating room.[3] At longer or shorter distances the intensity of radiation varies approximately inversely
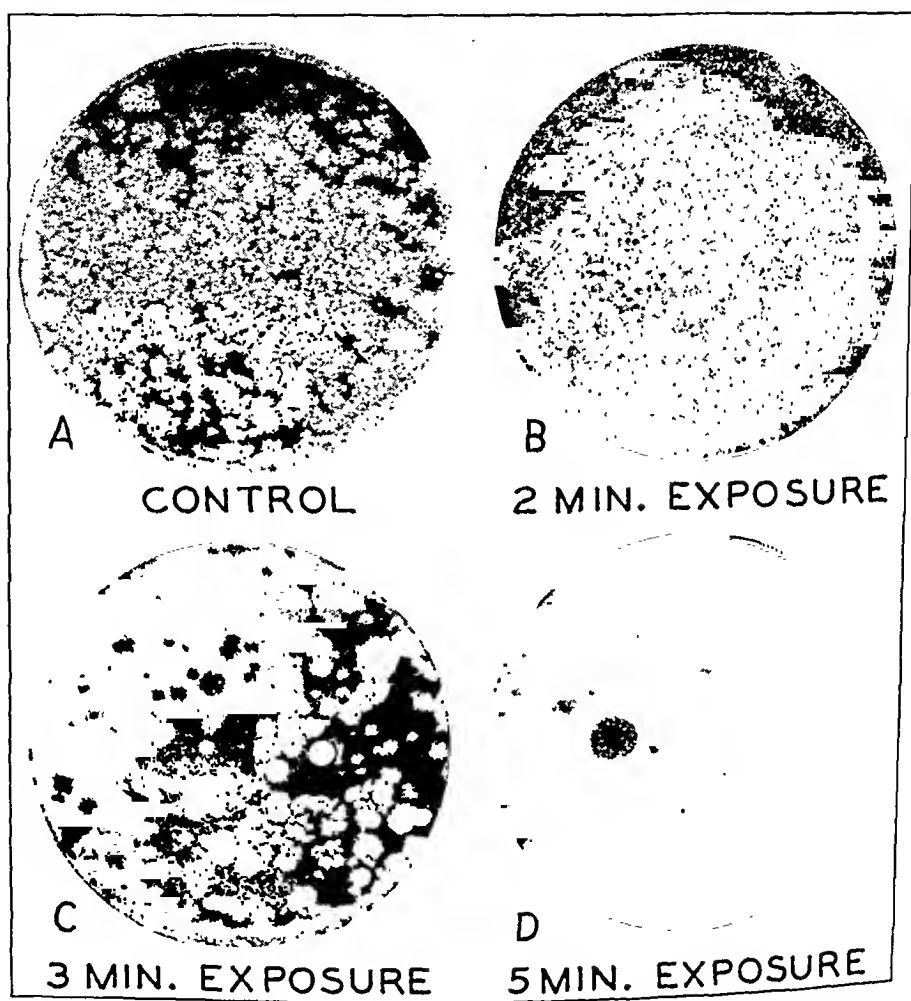
Fig. 4 (Mucor).—Photographs of a series of blood agar plates exposed as indicated in the descriptions of the foregoing illustrations. *A,* control plate; *B,* plate after irradiation for two minutes; *C,* plate after irradiation for three minutes; *D,* plate after irradiation for five minutes. Mucor and Monilia were the least resistant of the fungi tested (table 2).

as the square of the distance from the source of radiation and may be compensated by variations in the output of the unit. (Further studies are being carried on with the help of Mr. D. G. Sharp, their object being

the more accurate determination of the amount of energy from this irradiation unit required to kill various bacteria floating in the air.)

MATERIAL AND METHOD

Cultures of the bacteria listed in table 1 were prepared as follows: A fresh twenty-four hour broth culture was diluted 1:10,000 with sterile water, and the solution was placed in an atomizer. Twenty blood agar plates (p_H, 7.4) were

A CONTROL   B 5 MIN. EXPOSURE

C 10 MIN. EXPOSURE   D 20 MIN. EXPOSURE
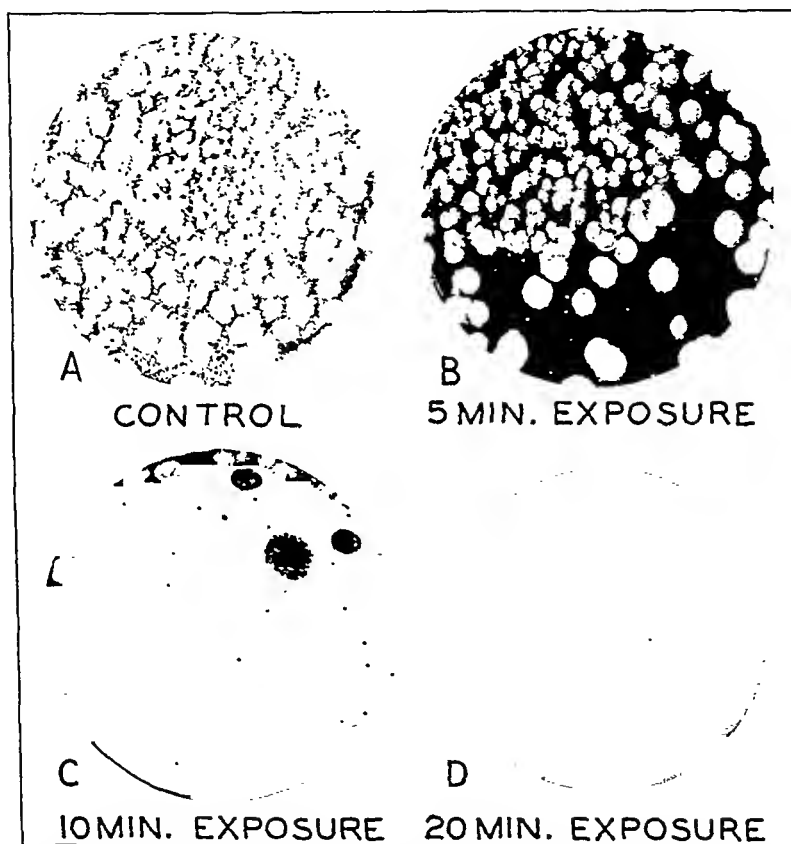
Fig. 5 (Geotrichum).—Photographs of a series of blood agar plates exposed as indicated in the descriptions of the foregoing illustrations. *A*, control plate; *B*, plate after irradiation for five minutes; *C*, plate after irradiation for ten minutes; *D*, plate after irradiation for twenty minutes. Some colonies of Dematium, Penicillium and Cladosporium survived an exposure of ten minutes, but all were killed by an exposure of twenty minutes (table 2). As in the case of the bacteria, the colonies at the periphery of the plate, which were shaded from part of the radiation by the upright edge of the Petri dish, survived longest.

sprayed at a distance of 12 inches (30 cm.) with each type of organism. Five of the twenty plates were used as controls to show the density of inoculation.

The remaining plates were exposed to radiation from a unit of eight tubes [5] (for arrangement of the tubes, see legend to figure 1) at a distance of 5 feet (150 cm.) from the individual tubes for periods of one, two and three minutes. This allowed five plates for each period of exposure. All plates were then incubated for forty-eight hours at 37.5 C.

The average number of colonies per Petri dish for the controls and for each period of exposure are shown in table 1. The values given in this table, particularly those designated by the word "innumerable," can be compared with photographs of a single control plate and a series of exposures of Staphylococcus albus (fig. 1), Bacillus pyocyaneus (fig. 2) and Bacillus subtilis (fig. 3).

It will be noted both in table 1 and in the photographs that there are variations in the susceptibility of different organisms. We do not wish to emphasize these variations or draw any conclusions until more accurately controlled experiments are completed, but we do wish to emphasize the fact that a large percentage of every type of bacteria tested were killed by relatively few minutes of exposure. From these and other tests we know that for this density of inoculation and with this intensity of radiation, sterilization reaches a level of over 95 per cent after three minutes of exposure. Some of the variations shown in the table may be dependent on the density of inoculation, but different organisms with the same density of inoculation still show variations in the time required for sterilization, indicating a difference in their resistance.

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5. In a previous publication [3] it has been shown that a blond person can be exposed to this intensity of radiation (approximately 28 to 30 microwatts per square centimeter of radiation at 2,537 angstrom units, this being over 80 per cent of the total radiation from the tubes) for eighty minutes without an appreciable burn. There are a prickly sensation and some redness of the skin, which clears within twenty-four hours. In over 1,000 operations, some performed with a much greater intensity of radiation, no patient has received an appreciable burn and no patient has had any complaint which could be ascribed to the irradiation (Hart, D.: Sterilization of the Air in the Operating Room by Bactericidal Radiant Energy: Results in Over Eight Hundred Operations, Arch. Surg. 37: 956 [Dec.] 1938; Sterilization of the Air in the Operating Room with Bactericidal Radiation: Comparative Analysis of One Hundred and Thirty-Two Individual Stages of Extrapleural Thoracoplastics Performed with Radiation and One Hundred and Ten Stages Performed Without Radiation, J. Thoracic Surg. 7:525-535 [June] 1938). Over 100 experiments on animals have shown that wounds exposed to this intensity of radiation for from ten to ninety minutes healed as well as those of the controls, if not better (Hart, D., and Sanger, P. W.: Effect on Wound Healing of Bactericidal Ultraviolet Radiation from a Special Unit: Experimental Study, Arch. Surg., this issue, p. 797).

Cultures of the fungi tested (table 2) were prepared as follows: A fresh transplant of each was made to a Sabouraud slant and allowed to grow at room temperature. When the growth covered the slant completely, sterile water was added to fill the tube and an emulsion was made. The resulting emulsion was

TABLE 1.—*Effect of Ultraviolet Radiation* * *on Various Bacteria*

Bacterium	Average Number of Colonies† per Plate			
	Control	1 Minute	2 Minutes	3 Minutes
Staph. albus.............................	Innumerable	66	15	2
Staph. citreus...........................	160	102	35	6
B. proteus...............................	Innumerable	61	7	2
B. pyocyaneus...........................	Innumerable	Innumerable	200	38
B. coli..................................	Innumerable	Innumerable	Innumerable	8
Str. haemolyticus beta..................	Innumerable	98	53	12
B. subtilis..............................	Innumerable	Innumerable	220	42
K. pneumoniae (Friedländer's bacillus)..	Innumerable	110	100	19

* Over 80 per cent of the output was at 2,537 Å. The intensity of radiation was from 23 to 30 microwatts per square centimeter.

† The number of colonies surviving each period of exposure was somewhat increased by partial shading of the periphery of the plate by the upright edge of the Petri dish (figs. 1, 2 and 3).

TABLE 2.—*Effect of Ultraviolet Radiation* * *on Various Fungi*

Fungus	Average Number of Colonies† per Plate							
	Control	1 Min.	2 Min.	3 Min.	5 Min.	10 Min.	20 Min.	60 Min.
1. Monilia................	Innumerable	200	150	45	0	0	0	0
2. Mucor.................	Innumerable	Innumerable	Innumerable	60	25	0	0	0
3. Geotrichum..........	Innumerable	Innumerable	Innumerable	Innumerable	180	20	0	0
4. Dematium............	Innumerable	Innumerable	Innumerable	Innumerable	Innumerable	Innumerable	0	0
5. Penicillium..........	Innumerable	÷	÷	÷	÷	÷	0	0
6. Cladosporium........	Innumerable	÷	÷	÷	÷	÷	0	0
7. Aspergillus..........	Innumerable	Innumerable	Innumerable	Innumerable	Innumerable	Innumerable	70	50

* Over 80 per cent of the output was at 2,537 Å. The intensity of radiation was from 28 to 30 microwatts per square centimeter.

† The number of colonies surviving each period of exposure was somewhat increased by partial shading of the periphery of the plate by the upright edge of the Petri dish (figs. 4, 5 and 6). The greater resistance of fungi as compared with bacteria may be accounted for in part by their tendency to form clumps which cannot be readily broken up. Aspergillus, which has a large amount of pigment and normally grows in the sunshine, was by far the most resistant fungus tested.

diluted 1:2,000 and was placed in an atomizer. Eight Sabouraud plates were sprayed with each emulsion at a distance of 12 inches (30 cm.). One plate was used as a control, and the remainder were exposed to the same intensity and spectral distribution of radiation as was used for the bacteria. Irradiation was

continued for one, two, three, five, ten, twenty and sixty minutes (except for Cladosporium and Penicillium, which were counted only after exposure for twenty and sixty minute periods, previous tests with these two organisms having shown that plates sprayed with them are not sterilized by an exposure of ten minutes).

The results are shown in table 2, which may be compared with the photographs of a single control and a series of exposures of Mucor (fig. 4), Geotrichum (fig. 5) and Aspergillus (fig. 6).
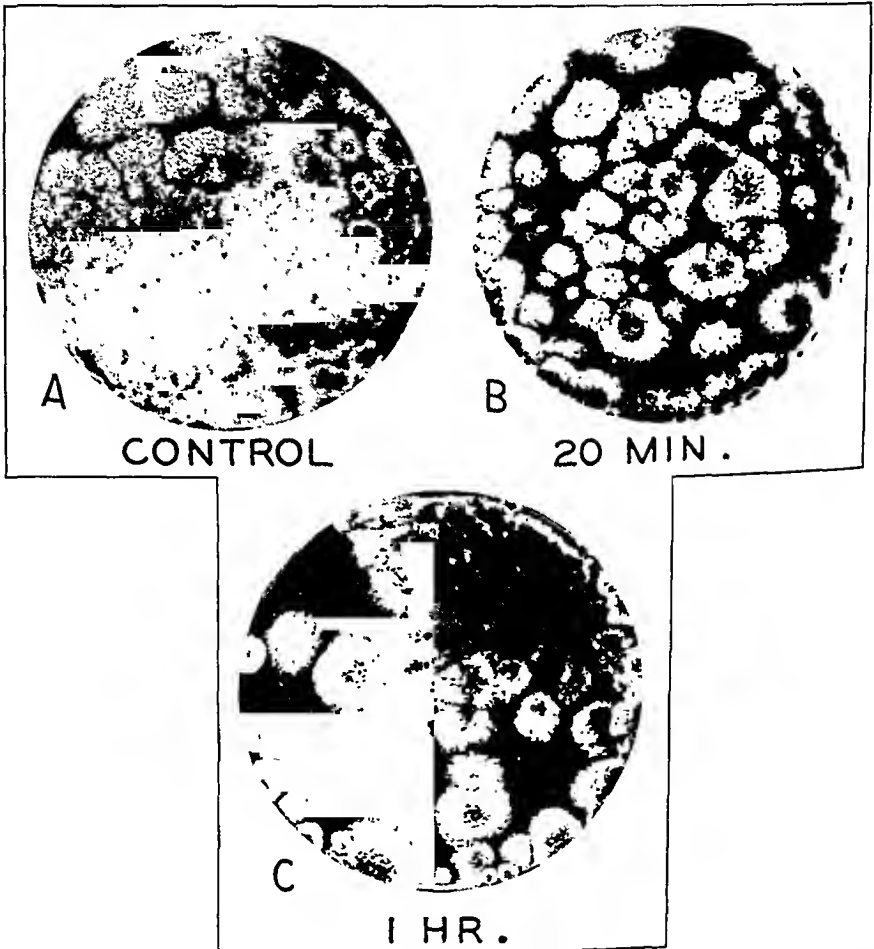
Fig. 6 (Aspergillus).—Photographs of a series of blood agar plates exposed as indicated in the descriptions of the foregoing illustrations. *A*, control plate; *B*, plate after irradiation for twenty minutes; *C*, plate after irradiation for one hour. This fungus, which normally grows in the sunshine, and contains a large amount of pigment, was the only one tested which was not killed by an exposure of twenty minutes. An exposure of sixty minutes had some effect, but many of the colonies survived.

SUMMARY

Various bacteria and fungi have been sprayed on culture plates and exposed to bactericidal radiation (over 80 per cent of the output of the irradiation unit being at 2,537 angstrom units [2]) at a distance of 5 feet

(150 cm.) from the center of the tubes. While the bacteria showed some variation in resistance, most of them were killed by an exposure of three minutes. The irradiation was also effective for killing fungi. Fungi were more resistant than the bacteria and varied widely in their susceptibility. Aspergillus (a nonpathogen), which grows in the sunshine and produces a large amount of pigment, was the most resistant; it was the only one which survived an exposure of twenty minutes, and some of its colonies survived an exposure of one hour. The tendency of fungi to grow in clumps may account in part for their greater resistance.

CONCLUSION

Special ultraviolet radiation (over 80 per cent of the output of the irradiation unit being at 2,537 angstrom units [2]) with low erythemic and high bactericidal properties, with a negligible production of ozone and heat and derived from a source which is relatively inexpensive for installation and operation, is highly efficient in killing many and possibly all bacteria and fungi at a distance of 5 feet (the intensity of radiation being 30 microwatts per square centimeter) and is a valuable contribution to the development of an aseptic surgical technic.

TUMOR OF THE BRAIN AS A CAUSE OF DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

A. LURJE, M.D.

MOSCOW, U. S. S. R.

Clinical studies and pathologic experiments have contributed to a broad investigation of the peripheral dystrophies associated with diseases of the brain.

Successive researches made in this domain (Schiff and Rokitansky;[1] Charcot;[2] Andral;[3] Arndt;[4] Mogilnitzky;[5] Burdenko;[6] Nikolajew;[7] Korst;[8] Cushing[9]) have laid the foundation for an original theory of the genesis of certain types of gastric and duodenal ulcer. This conception establishes a direct connection between the development of chronic ulcer and the destruction of the trophic centers. Experiments performed by Burdenko and Mogilnitzky,[10] Pigalew[11] and Skoblo[12] (from the laboratory directed by Speransky[13]) and consisting in infliction of various kinds of trauma on the region of the diencephalon have created a new basis for the aforementioned theory.

1. Schiff and Rokitansky, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 3.

2. Charcot: Léçons, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 579.

3. Andral, G.: Clinique médicale, ou choix d'observations recueillies à l'Hôpital de la charité (clinique de M. Lerminier), ed. 3, Paris, Crochard & Cie, 1840, vol. 5, p. 200.

4. Arndt, R.: Deutsche med. Wchnschr. 14:83, 1888.

5. Mogilnitzky, B. N.: Virchows Arch. f. path. Anat. 257:109, 1925.

6. Burdenko, N.: Ztschr. f. d. ges. Neurol. u. Psychiat. 148:343, 1933.

7. Nikolajew, cited by Burdenko.[6]

8. Korst, L.: J. sovrem. chir. 3:607, 1928.

9. Cushing, H.: Surg., Gynec. & Obst. 55:1, 1932.

10. Burdenko, N., and Mogilnitzky, B. N.: Ztschr. f. d. ges. Neurol. u. Psychiat. 103:42, 1926.

11. Pigalew, I. A.: Ztschr. f. d. ges. exper. Med. 82:617, 1932.

12. Skoblo, M. S.: Ztschr. f. d. ges. exper. Med. 73:57, 1930.

13. Speransky, A. D.: Elementry postroenja teory mediziny, Moskow, Wien, 1935.

As regards the pathologic picture presented by the autonomic nervous system in cases of peripheral dystrophy, Mogilnitzky, Sipovskiy [14] and also Zajewloschin and Rubinstein [15] have discovered phenomena of degeneration and irritation in the nervous elements of the solar plexus and of the cervical sympathetic ganglions in the presence of round ulcer, the alterations being mainly manifested in the solar plexus. The data obtained by Stöhr [16] and Rieder,[17] who have investigated the intramural autonomic nervous system (plexuses of Auerbach and Meissner) in the gastric wall in the presence of chronic ulcerous processes and found there a number of morphologic destructive alterations, may be used as additional evidence of the trophic origin of gastric and duodenal ulcer. Similar alterations in the intramural nervous system, as well as in the sympathetic ganglions associated with ulcerous processes of the intestine, have been detected by Wail. In the presence of some diseases associated with dystrophy, alterations in the central nervous system have also been found. Thus, in a number of cases of cerebral cachexia Shapiro [18] has discovered alterations (gliosis or neuronophagy) in the diencephalon. Stief [19] and also Peters [20] have observed degenerative alterations in the nuclei of the diencephalon in the presence of severe, exhausting diseases, such as progressive paralysis and cancerous cachexia. The data proving the existence of a close anatomic and functional connection between processes developed in the brain and processes developed in the peripheral autonomic nervous system led me to undertake a pathoanatomic study of the ganglions of the sympathetic trunk and the ganglions and trunks of the vagus nerve in cases of tumor of the brain. In the presence of a tumor of the brain the alterations of the cerebral tissue mainly involve the glia. The ganglionic elements in the close vicinity of the tumor exhibit considerable resistance. For instance, degenerative phenomena (disappearance of cells in the cortex) are detected only for a distance of some millimeters from the tumor. In all remaining regions the cells remain normal (Weber; [21] Casper [22]). Under the action of pressure the ganglionic cells near the tumor may change their form; they become flattened but keep the Nissl substance.

14. Sipovskiy, P. W.: Arch. pat. anat. i patol. physiol. **1:**102, 1935.

15. Zajewloschin, M. N., and Rubinstein, B.: Arch. pat. anat. i patol. physiol. **1:** 97, 1935.

16. Stöhr, P., Jr.: Ztschr. f. Zellforsch. u. mikr. Anat. **16:**123, 1932.

17. Rieder, W.: Deutsche Ztschr. f. Chir. **244:**471, 1935.

18. Shapiro: Trudy I Moskovskogo Meditsinskogo Instituta, 1936, vol. 6.

19. Stief, cited by Josephi, in Hirsch, M.: Handbuch der innere Sekretion, Leipzig, Curt Kabitzsch, 1929.

20. Peters, G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **154:**331, 1935.

21. Weber, cited by Casper.[22]

22. Casper, J.: Ztschr. f. d. ges. Neurol. u. Psychiat. **145:**208, 1933.

Some nerve fibers in the immediate vicinity of the tumor lose their myelin sheaths so that the axis-cylinders fall out, and some of them show fragmentation; the remote fibers remain intact. An intracranial tumor may influence in different ways the nuclei of the brain stem known as sympathetic and parasympathetic centers, as well as those of other regions and their conducting paths. These ways are the following: 1. Growth of the mass and destruction of the diencephalic nuclei or their conducting paths. This is the most important factor. 2. Compression of these formations by the growing tumor. Such compression may be caused by either a near or a distant tumor; however, the relative stability of the ganglionic elements and their resistance to the influence of the tumor at a distance allow one to assume that if the tumor is distant the peripheral changes will be relatively insignificant or will be absent. 3. Disease of the vessels supplying a certain region of the brain stem, followed by an infarction in the corresponding area. 4. Obstruction by the tumor of the paths of communication of the cerebrospinal fluid, followed by distention of the third ventricle and atrophy of its base, of the region of the tuber cinereum and of the nuclei corporum mamillarium in the region of the autonomic centers.

In describing peripheral diseases of the autonomic nervous system one must take into account the fact that clinical researches (Zakharchenko;[23] Tumskoy;[24] Blumenau[25]) indicate the presence of crossed fibers running from the diencephalic nuclei. Probably the crossing of vegetative fibers, as well as that of more highly differentiated descending systems such as the pyramidal tract, Löwenthal's tract or Monakow's tract, is not complete. Therefore, a pathologic process developing above the site of the crossing will also be more or less manifested on the side homolateral to its localization. In the spinal cord the descending autonomic systems apparently are partly or completely interrupted in Jacobson's centers of the lateral horns; they pass through the anterior roots of the rami communicantes to the sympathetic trunk, its ganglions and the prevertebral ganglions.

My pathoanatomic researches have been carried out on material obtained from 21 patients: 18 who died of tumor of the brain, 1 who died of meningitis, 1 who died of abscess of the cerebellum and 1 who died of hydrocephalus.

Tumors of the brain occurring in this series may be divided into the following types: glioma, 10; ganglioneuroma, 1; meningioma, 2; neuri-

23. Zakharchenko, M. A.: Sosudistye zabolevanja mozgovogo stvola, Moskow, G. F. Smirnov, 1911.

24. Tumskoy, V. A.; Ostapovitsch, G. D., and Semenov, S. S.: Kazan, m. j. 28:97, 1933.

25. Blumenau, L. W.: Anatomo-physiol. vvedenie v clinicu nervnich bolezni, Moskow, Gosisdat, 1925.

noma, 1; metastatic sarcoma, 1; metastases from carcinoma, 3. I have investigated both superior cervical ganglions, the stellate ganglions, the solar plexus and the trunks of the vagus nerve and its ganglion nodosum; in a number of cases vagal nuclei of the medulla and nuclei of the hypothalamic region have been studied. I have applied the method of staining the frozen sections described by Filatowa and Lawrentjew [26] after Bielschowsky and Gros. Some preparations have been after-stained with hematoxylin or sudan. In some cases I have stained the myelin by the method of Spielmeyer; the cells have been stained according to Nissl's method.

As for my microscopic observations, in 4 cases I saw on the autopsy table phenomena which may be considered dystrophic: hemorrhage in the gastric wall in 2 cases and agonol autolysis of the gastric and esophageal walls in 2 cases. In the brains of the 4 cadavers I observed the brain stem invaded by the tumor in 2 instances; in 2 instances the brain stem was under considerable pressure.

Zenker [27] and Brosch [28] have also noticed autolysis of the gastric and esophageal walls in cases of disease of the brain stem.

It is necessary to point out that dystrophic alterations at the periphery have not always been followed by changes in the sympathetic ganglions. In 2 instances I observed peripheral trophic disturbances in the form of hemorrhage in the gastric wall and agonal autolysis of the gastric wall without any considerable alteration in the solar plexus. Obviously, dystrophic changes in the digestive tract may occur without morphologically visible disease of the collectors of autonomic innervation. A deeper and more prolonged dystrophic process, such as penetrating or perforating gastric ulcer, is followed by alterations of the nervous system similar to those observed in cases of tumor of the brain. This is most obvious in the study of the solar plexus.

Among the pathologic phenomena observed in the solar plexus, the attention is drawn by the *Kugelphänomen,* the formation of peculiar thin rings and small "loops." These formations are caused by breaking down of the pericellular apparatus, destruction of the neurofibrillar cellular apparatus, pyknotic alterations of the nucleus, formation of swellings or varicosities on the fibers and vacuolation and disaggregation of the fibers. Disease of the fibers and cells in the solar plexus has been observed much less frequently than in the ganglions of the sympathetic trunk and mainly in cases of cancer.

26. Filatowa, A. G., and Lawrentjew, B. I.:   Virchows Arch. f. path. Anat. 286:1, 1932.

27. Zenker, in von Ziemssen, H.:   Handbuch der speziellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1877, vol. 7.

28. Brosch, cited in Henke. F., and Lubarsch, O.:   Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

A considerable development of the *Kugelphänomen* in the solar plexus has been discovered in 8 cases of tumor of the brain. In the vicinity of some cells from two to five *Kugeln* may be seen. Besides those detected in the immediate proximity of the cells, some isolated *Kugeln* have been observed among the bundles of fibers. In 5 cases, together with the *Kugeln* I have detected hollow "rings;" in some they were connected with fibers and formed small "loops" (figs. 1, 2 and 3).

In these 5 cases I have observed invasion or compression of the brain stem by the tumor on the level of the anterior part of the medulla oblongata and the pons.
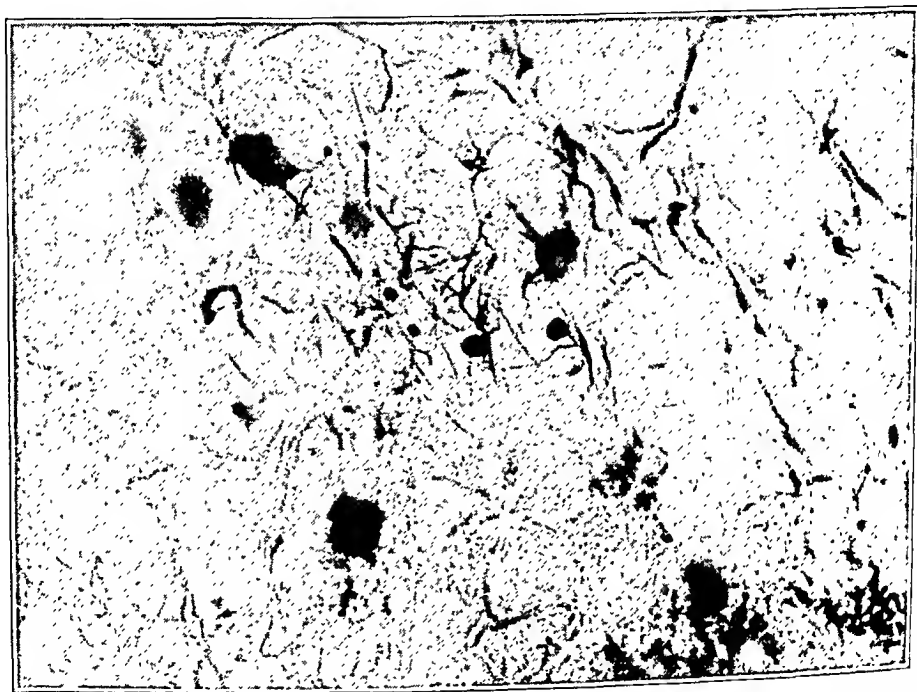
Fig. 1.—Photomicrograph of *Kugelphänomen* observed in the solar plexus of a patient with tumor of the pineal gland. Gros-Bielschowsky stain; Zeiss ocular 4 Ob. D.

In 10 cases the *Kugelphänomen* was slightly developed. In 2 of these cases compression of the medulla was observed. As some of the patients in whom a small number of *Kugeln* were detected were much older than the majority of those in whom *Kugeln* were more numerous, one cannot consider this pathologic phenomenon exclusively a sign of age involution. One may consider, as a control, preparations of the solar plexuses of patients with disease of the lungs, in which the *Kugelphänomen* has also been rarely found. For comparison, I stained the semilunar ganglions of 2 patients with cancer of the stomach, of 1 with cancer of the biliary passages and of 2 with gastric ulcer (1 of these died from shock while I was isolating an ulcer penetrating into the pancreas;
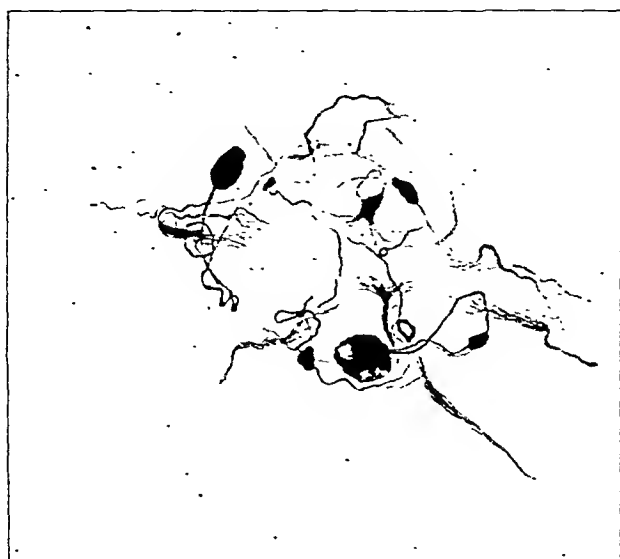
Fig. 2.—Drawing of *Kugeln* and "Rings" observed in the solar plexus of a patient with a tumor of the cerebellum. Gros-Bielschowsky stain; Zeiss homogeneous immersion.
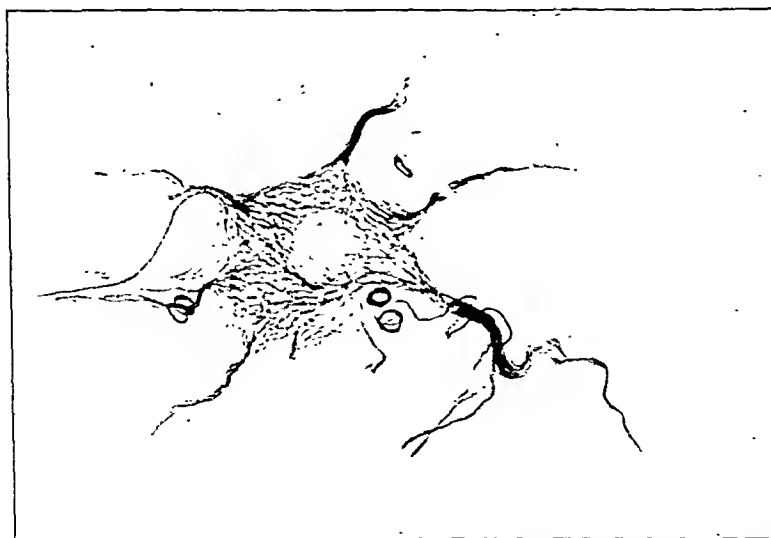
Fig. 3.—Drawing to show the breaking down of the pericellular apparatus of the right stellate ganglion in a patient with tumor of the occipital lobe. Gros-Bielschowsky stain; Zeiss homogeneous immersion.

another, with a perforating ulcer of six hours' duration, died from aspiration of the vomited matter on the first day after operation).

The most marked development of the *Kugelphänomen* was observed in cases of cancer of the biliary passages. The whole visual field was speckled with *Kugeln,* a picture which probably was connected with invasion and destruction by the tumor of a great number of postganglionic trunks passing inside the hepatoduodenal ligament. In other cases the *Kugelphänomen* was less developed but rather marked. Particular interest was afforded by the presence of a great number of "loops" and "rings" in preparations of the solar plexus of a patient with a perforating ulcer, the loops and rings having the same form but being more numerous, as in the aforementioned cases of the tumor of

Fig. 4.—Drawing of "rings," derivatives of the synapses, in the celiac ganglion in a case of ulcus ventriculi perforans. Gros-Bielschowsky stain; Zeiss homogeneous immersion.

the brain (fig. 4). It is possible that this coincidence is the result of a kind of qualitative standardization of the morphologic reaction of the solar plexus to pathologic impulses in general, that is, impulses received from the center as well as from the periphery. It may be that confirmation of the theory (Lancereux;[29] Vulpian,[30] Burdenko) of the neurogenic central genesis of some forms of round ulcer lies in this uniformity of reaction of the solar plexus in cases of tumor of the brain and peripheral disease (gastric ulcers and cancer of the stomach).

29. Lancereux: Gaz. d. hôp. **49**:314, 1876.
30. Vulpian, E. F. A.: Léçons sur l'appareil vaso-moteur (physiologie et pathologie), Paris, Germer-Baillière, 1875, vol. 1.

It may be assumed that changes of central origin in the solar plexus at a certain stage of development, in the presence of additional irritation or without it, lead to peripheral dystrophy in the form of round ulcers. Frequently observed hyperhidrosis and pilomotor reactions, as well as symptoms of so-called vagotonia, indicate that in cases of gastric ulcer one must suspect processes of destruction in the autonomic nervous system. Apparently, the gastric ulcer may sometimes be a sign of disturbance of the peripheral trophic action as a result of disorders of the central region of the vegetative system, not always accessible to the rough methods available for morphologic investigation. In the ganglions of the sympathetic trunk the changes did not differ qualitatively from

Fig. 5.—Photomicrograph of varicose fibers of the left stellate ganglion, observed in a patient with a tumor of the cerebellopontile angle. Gros-Bielschowsky stain; Zeiss ocular 7 Ob. D.

those in the solar plexus. Pathologic changes were observed (particularly in cases of primary tumors of the brain) in fibers and in stellate ganglions, which are the most important collectors of autonomic innervation. Alterations of the fibers were found at different stages of development, from the appearance of varicosities and the formation of vacuoles to complete disintegration. The affected fibers exhibited a group arrangement; they also formed bundles (figs. 5 and 6). In cases of tumor of cortical or subcortical localization in the temporoparietal or occipital region (3 cases) the fibers were symmetrically affected on the side of occurrence of the tumor as well as in the ganglion of the opposite side. Peripheral alterations of the fibers in the ganglions obvi-

ously occur as a result of disease of the autonomic nerve paths emerging from the affected zone. One may assume that not all these paths are crossed. Thus, the pathologic impulse from the cortex is transmitted more or less uniformly to both stellate ganglions. The predominance of crossing phenomena and the occurrence of alterations in the fibers in 1 case of tumor, in which the growth destroyed the internal capsule and exerted pressure mostly on the hypothalamic region of one side, confirm the presence of crossing of the vegetative paths in the brain stem below the hypothalamic region. This case leads me to suppose that the majority of the fibers of the affected central vegetative pathway
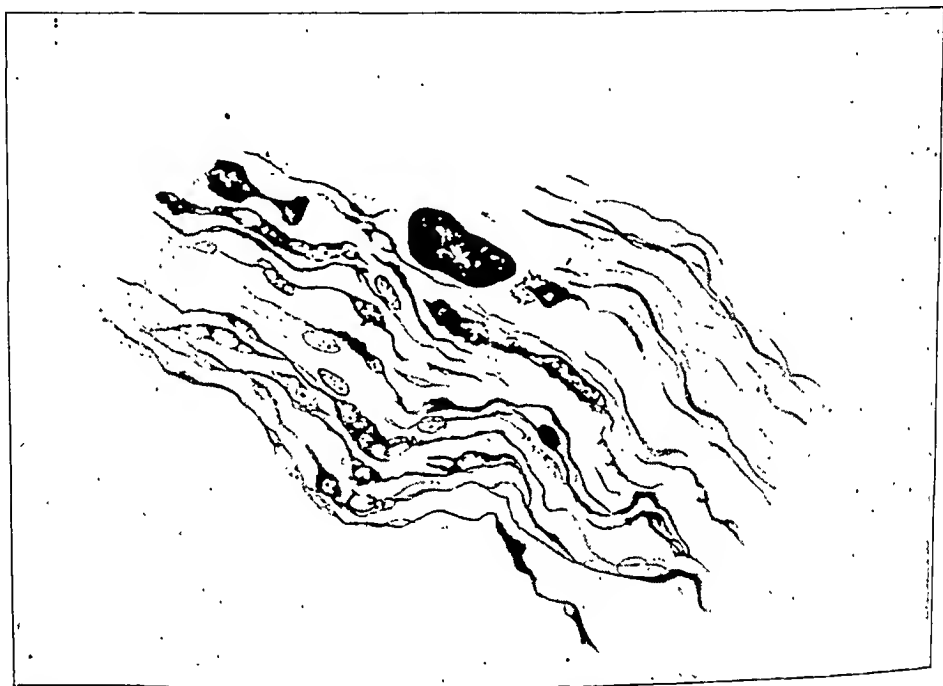
Fig. 6.—Photomicrograph showing the disaggregation of fibers in a patient with a tumor of the cerebellopontile angle; Zeiss ocular 7 Ob. D.

arising in the hypothalamic region take part in crossing. The prevailing homolateral character of the alterations in the fibers of the stellate ganglions when the central disease is localized in the pons and the more caudal regions of the brain stem (2 cases) confirms the statement that crossing in the autonomic conducting paths takes place mainly somewhere caudad to the hypothalamic region, so that a considerable number of these fibers run in the region of the pons after having been crossed. Disease of the system below the crossing produces peripheral radiation on the same side.

Probably only a small number of the fibers of the autonomic pathway cross below, in the medulla, which may be the cause of alterations in the fibers (although found in a much smaller number) also in the

contralateral stellate ganglion in cases of localization of the tumor at the level of the pons. The influence of the tumor on the vermis in 2 cases was followed by symmetric alterations in the fibers of the autonomic nervous system. The disease is probably associated with disease of some central neurons of the autonomic system. The localization of the cell bodies of these neurons is imputed to the cerebellum by a number of authors (Mikhilson and Tihalskaja).[31]

In cases of frontal tumor, of which there were 3, and in 1 case of supracerebellar subtentorial tumor, because of the relatively great distance of the tumor from the autonomic centers of the diencephalon and the brain stem and their pathways and because of the resistance of the latter to the action of the distant tumor, I did not observe any alterations in the preganglionic systems of the fibers in the sympathetic ganglions.

In the fibers and in the nuclei of the vagus nerve in cases of unilateral localization of the disease of the diencephalon and the pons, the alterations were manifested for the most part contralaterally (3 cases). This probably occurred as a result of crossing of the thalamonuclear pathways descending to the nuclei of the vagus nerve in the medulla at a relatively low level, above the zone of localization of these nuclei. Thus, in my cases the central paths had been affected before the fibers passed to the other side. The pathologic stimulus provoking irritation and degeneration apparently passes through the synapses to the cells of the nuclei dorsales et ambiguui of the vagus nerve and then to the axons of these cells.

In these 2 cases I observed peculiar pyknomorphous alterations in the cells of the dorsomedial nuclei of the vagus nerve on the side opposite the tumor; they diminished in size and lengthened (figs. 7 and 8). The alterations detected in the fibers of the sympathetic ganglions and the trunk of the vagus nerve are not at all qualitatively specific for cases of brain tumors. There is only one particularity to be noticed, namely, the aforementioned relative quantitative lateralization of the process (its unilateral development).

In my material, in the presence of a primary tumor of the brain arising from its supporting tissues, elements of generalized intoxication resulting from disintegration of the tumor, such as are observed in general infections in cases of cancer, were almost absent. In no case have I observed acute or chronic processes in the internal organs which might be considered factors in the development of alterations in the sympathetic fibers. My own material, obtained from investigation of the sympathetic ganglions in cases of pulmonary abscess and suppurative

31. Mikhilson, A. I., and Tihalskaja, W.: Russk. phy. j. **16**:466, 1933.

bronchiectasis, shows few alterations and allows me to establish relative persistence of the sympathetic fibers.

I cannot state that there is any relation of the alterations observed in the peripheral autonomic system in my material to surgical intervention. There was an exception in 1 case, in which after dissection of the vermis considerable alterations were observed in the fibers.

For a more detailed study of the influence of surgical trauma I have performed a trephination of the skull in the temporoparietal region in 7 dogs. Mixed anesthesia was used, ether, chloroform and alcohol being employed. After section of the dura mater, glass sticks were introduced under the tuber cinereum in 4 dogs and under the temporal
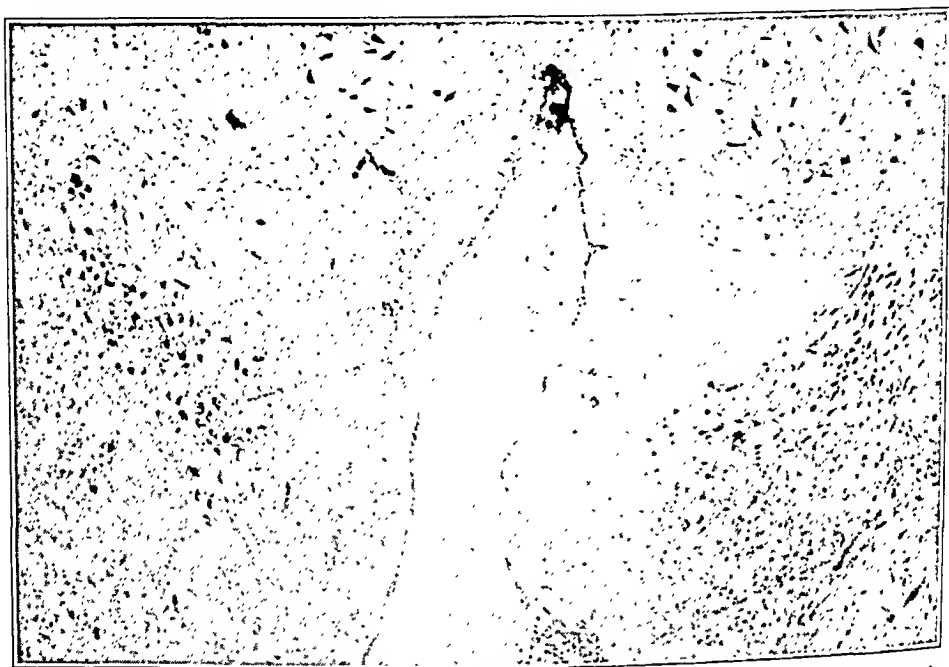
Fig. 7.—Photomicrograph of the base of the fourth ventricle. Note the invasion of the left half of the brain stem by the tumor at the level of the pons. Nissl stain; Zeiss ocular 7 Ob. A.

lobe near the tuber cinereum in 3 dogs. Three animals died three days after operation (1 from meningitis), and 4 animals were killed after periods varying from nine to fifteen days. In 2 dogs I discovered an insignificant number of varicose fibers in the trunks of the vagus nerve. In all the dogs the fibers of the sympathetic ganglions were observed to be normal, although 1 of the animals had a round duodenal ulcer and 2 had a hemorrhage in the mucous membrane of the small intestine. The last circumstance makes me emphasize the relative resistance of the fibers of the sympathetic ganglions to the pathologic influence. As regards the hydrocephalus, I attribute only an insignificant role to that

factor because of the aforementioned resistance. This is confirmed by the fact that in 3 cases in which considerable hydrocephalic changes were observed there was almost no reaction of the preganglionic systems of the fibers. Thus, the probable cause of the alterations detected in the fibers in my cases was disturbance of the central neurons of the autonomic nervous system by the tumor, which resulted in involvement of the concomitant peripheral neurons.

I have discovered in 2 patients a considerable number of *Kugeln* in the ganglion nodosum of the vagus nerve on the side of localization of the process in the brain; in the vicinity of some cells five or six *Kugeln* have been found.
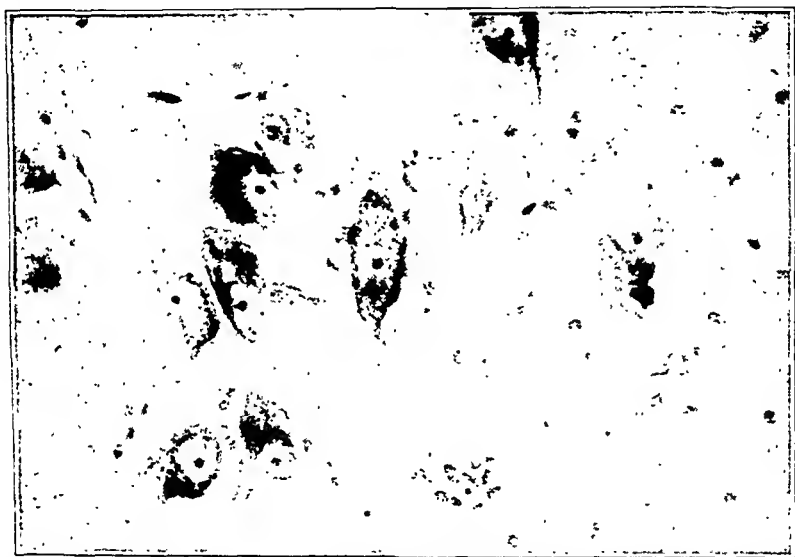
Fig. 8.—Photomicrograph of the nucleus dorsomedialis of the left vagus nerve (side of localization of the tumor). Nissl stain; Zeiss ocular 7 Ob. D.

In the first case one must suppose that because of a stronger compression of the root of the vagus nerve on the side of occurrence of the abscess, the axons of the cells of the corresponding ganglion nodosum were affected and a homolateral *Kugelphänomen* was considerably developed. Homolateral development of the *Kugelphänomen* in the ganglion nodosum was observed in 1 patient with bronchiectasis mainly on the side on which the lung was affected. Several hours before death an injection of procaine hydrochloride was made into the trunk of the vagus nerve, and a lobectomy was performed.

In cases of cancerous metastases, in which degenerative phenomena have been most frequently observed, an accumulation of satellites occasionally was detected around the degenerated cells.

As regards malignant tumor, it must be emphasized that alterations in the fibers and cells may be caused in a great measure by generalized toxic or reflex influences associated with the disintegration and, in fact, with the very existence of the cancerous neoformation, as has been observed by Borowsky.[32] In 3 cases I observed an increased deposit of argentophilic pigment in the nerve cells of the sympathetic ganglions in persons from 12 to 24 years of age.

Herzog,[33] De Castro[34] and Chodos[35] stated that the increased accumulation of pigment is associated with diseases causing generalized exhaustion. Symptoms of such exhaustion, which pathogenetically may somewhat resemble cerebral cachexia, were also observed in my patients.
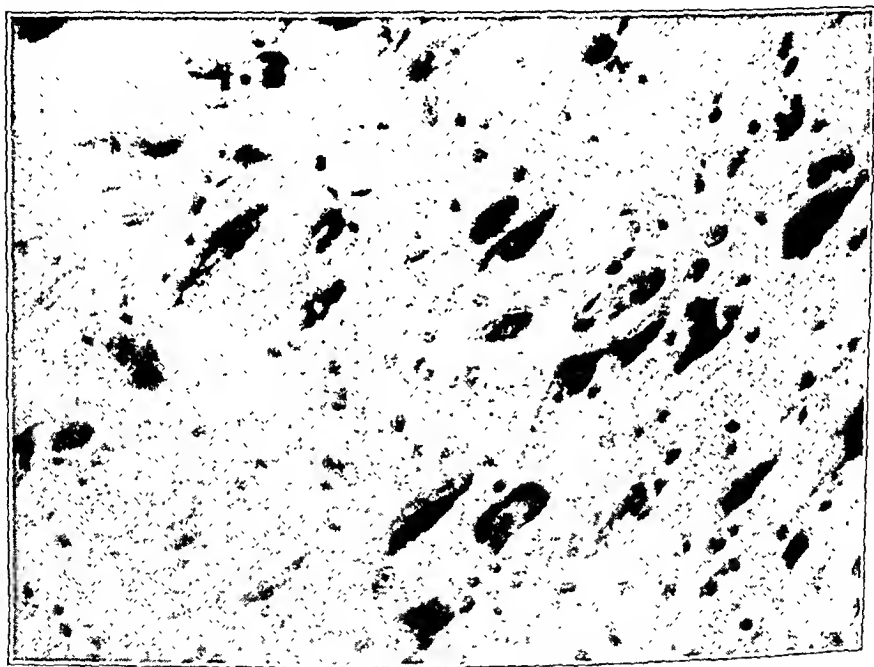
Fig. 9.—Photomicrograph of the nucelus dorsomedialis of the right vagus nerve (contralateral to the tumor). Nissl stain; Zeiss ocular 7 Ob. D.

Nevertheless, in other cases, in which little pigment was found in the cells of patients with generalized exhaustion, I had apparently to deal with an individual instability of metabolism in the nerve cells.

In 4 patients with tumors of the brain I have discovered single vacuoles and coarseness of the fibrillar structure in the cells. Very rarely (one in a preparation or in several preparations) I have observed

32. Borowsky, M. L.: Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:692, 1933.
33. Herzog, E.: Ztschr. f. d. ges. Neurol. u. Psychiat. **103**:1, 1926.
34. De Castro, F.: Sympathetic Ganglia, Normal and Pathological, Madrid, 1927.
35. Chodos, C. G.: Ztschr. f. d. ges. Neurol. u. Psychiat. **135**:358, 1931.

cells entirely filled with vacuoles, changed and degenerated. Some of the diminished cells had pyknotic nuclei and pale protoplasm.

In 6 cases of intracranial tumors with rather strongly manifested irritation and degeneration of the preganglionic fibers in the stellate ganglions I have detected phenomena of perinuclear tigrolysis, as well as of complete tigrolysis with group arrangement of the altered cells. In a lesser degree these phenomena in the ganglionic cells have been noticed by me in other patients with cerebral disease.

In the aforementioned experiments I observed in all cases a well marked perinuclear tigrolysis and sometimes complete tigrolysis. No lateralization of the process similar to that observed in disease of the fibers could be found in the arrangement of cells with tigrolysis. This circumstance, together with the lability of the tigroid substance in the nerve cells and a pheochrome type of granulation, leads me to attribute the phenomenon of tigrolysis to the general influence of the tumors on the vegetative centers, the surgical intervention, hunger and possibly other factors which may have escaped my attention.

SUMMARY

1. Phenomena of degeneration and irritation in the neural elements of the solar plexus are found mostly in cases of disease of the brain stem and are not always followed by dystrophic alteration of the tissues.

2. The qualitative features of the pathologic changes observed in the sympathetic and parasympathetic systems in the presence of tumor of the brain do not differ from those observed in the same regions of the nervous system in cases of disease of the peripheral organs.

3. In case of localization of the tumor in the region of the pons the changes in the fibers of the sympathetic ganglions are revealed mostly in the ganglions on the side of localization of the intracranial tumor.

4. In case of cortical localization of the tumor of the temporoparietal region, as a result of a partial crossing of cortical descending systems the changes exhibit symmetry.

5. In 1 case of hypothalamic tumor, neoformed alterations of the fibers prevailed in the stellate ganglion of the side opposite the tumor.

6. The alterations in the cells of the autonomic system exhibited a focal character and maintained a certain symmetry in the qualitative development of the process.

7. As a result of a low localization of the crossing of cortical and thalamonuclear pathways in cases in which neoformations were localized in the brain stem the fibers of the vagus nerve were for the most part affected contralaterally.

FRACTURES OF THE PELVIS

ANALYSIS OF SEVENTY-NINE CASES

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This is a review of cases in which fracture of the pelvis was treated at the Harlem Hospital from Dec. 1, 1933 to Dec. 1, 1937. It is a continuation of a study made by Conway.[1]

CAUSE OF INJURY

Seventy-nine patients with fracture of the pelvis, were admitted to the hospital within the period mentioned. Of these, 55 were males and 24 females, the ages ranging from 3 to 83 years. The age incidence is given in table 1.

It will be noted that the greatest number of patients entered the hospital when they were within the decade from 20 to 30 years. This decade is the most active period of life, when the patient is most susceptible to trauma.

The causative traumas are listed in table 2.

In this series, 39 patients were admitted to the hospital after having fallen or jumped from a height, such as a roof, fire escape, a window (first to fifth story), a flight of stairs or an elevator shaft. The second most important factor in causation of fractures of the pelvis is the automobile. Twenty-eight of the patients had been struck by an automobile. In 4 cases the cause of fracture was unknown; in these the patient's condition was so serious that he was unconscious when admitted, or was under the influence of alcohol. In 1 case the fracture was caused by a gunshot wound in which there were multiple perforations of the left ilium, the bladder also being punctured. The patient in this case died four days later from peritonitis even though a laparotomy was done to close the vesical openings. Four patients had crushing injuries. One was caught between two "L" cars and had other multiple

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1. Conway, F. M.: Fractures of the Pelvis: Clinical Study of Fifty-Six Cases. Am. J. Surg. **30**:69 (Oct.) 1935.

fractures. One patient was injured by the overturning of an automobile in which he was riding. One patient was struck with a steam bucket weighing 3 tons while he was handling coal. One patient had been assaulted.

ASSOCIATED INJURIES

In many cases of fracture of the pelvis the patient is unconscious, and roentgenograms of the entire osseous system are necessary. Complications, such as intracranial injuries and internal thoracic and abdomi-

TABLE 1.—*Age Incidence in Seventy-Nine Cases of Fracture of the Pelvis*

Age, Years	Number of Patients
1 to 10	6
10 to 20	13
20 to 30	20
30 to 40	12
40 to 50	19
50 to 60	4
60 to 70	2
70 to 80	1
80 to 90	1

TABLE 2.—*Causes of Fracture in This Series of Cases*

Cause	Number of Cases
Patient jumped or fell from a height	39
Patient struck by auto (taxicab, private car, motorcycle, truck)	25
Cause unknown	4
Patient shot	1
Patient caught between "L" cars	1
Patient fell from truck; run over by wheels	1
Patient injured in overturning automobile	1
Patient run over by wagon	1
Patient struck by coal bucket (3 tons)	1
Patient assaulted	1
Patient struck by subway train	1
Total	79

nal injuries, must be considered. Patients admitted to the hospital in a state of shock must be treated for shock even before treatment is given for fracture of the pelvis or associated fractures.

ANATOMIC CLASSIFICATION

In the anatomic classification of the fractures in this series of cases the terminology of Noland and Conwell has been followed (table 3).

PERIOD OF HOSPITALIZATION

Twenty-six of the 79 patients had fractures of the pelvis only; that is, there were no associated injuries. Of these 26, 2 had diabetes. We

are sure that this condition prolonged their stay in the hospital. However, including these 2 patients, for whom the period of hospitalization was fifty-two and eighty-four days respectively, the average period of hospitalization was twenty-six days. If these 2 patients are eliminated the average period of hospitalization for each of the remaining 24 patients was twenty and eight-tenths days (table 4). On the other hand, the average period of hospitalization for patients with fracture of the pelvis with associated injuries was forty-eight and three-tenths days. In other words, it was usually the associated injury and not the pelvic fracture which caused the prolonged hospitalization.

DIAGNOSIS

There is a definite method of examination to determine whether a fracture of the pelvis is present. With the patient in the recumbent

TABLE 3.—*Anatomic Classification of Fractures*

Injury	Left	Right
Fracture of ala of ilium...	7	7
Fracture of crest of ilium..	3	4
Fracture of superior ramus of pubic bone...........................	25	24
Fracture of inferior ramus of pubic bone...........................	21	13
Fracture of inferior ramus of ischium..............................	5	2
Fracture of superior ramus of ischium..............................	2	1
Fracture of acetabulum	6	6
Definite sacroiliac separation.....................................	4	4
Separation of symphysis pubis......................................		8
Isolated fracture of the ischial tuberosity........................		0
Double vertical fracture of the pelvis (Malgaigne).................		3
Fracture of the sacrum with associated pelvic fracture.............		7

position, one presses down on the anterior superior spines, or, by alternating this pressure, one rocks the pelvis. Pressure medially on the crests of the iliums or pressure directly downward over the symphysis pubis may, by eliciting pain, give a fairly definite indication as to whether or not a fracture exists. For fracture in the region of the acetabulum, by elevating, lowering, abducting, adducting, externally rotating and internally rotating the lower extremity one may obtain a fair idea of any existing pathologic condition. However, the final diagnosis depends on roentgen study, which certainly is a safer procedure.

DIAGNOSIS OF ASSOCIATED VISCERAL INJURY

When a patient has fallen from a third or fourth story window or who has been struck by an automobile, bloody urine is indicative of a pathologic condition which may exist anywhere along the genitourinary tract, from the kidney to the glans penis. Frank blood is passed in the presence of rupture of the urethra. If an attempt is made to pass a

TABLE 4.—*Uncomplicated Fracture of the Pelvis*

Patient	Age	Sex	How Injured	Type of Pelvic Injury	Days in Hospital	Result
M. G.	22	M	Struck by truck	Fracture of ascending ramus of left pubic bone at junction with ischium; fracture of sacrum near sacroiliac articulation	22	Improved
N. M.	7	M	Struck by automobile	Fracture of ascending ramus of right pubic bone at junction and ischium; relaxation of right sacroiliac joint	18	Improved
M. A.	20	M	Fell from roof	Transverse fracture of midportion of right ilium	1	Unimproved; transferred
P. B.	23	M	Automobile overturned with patient	Fracture of right side of symphysis pubis	7 AOR*	Improved
J. J.	25	M	Fell ten stories	Fracture of right ilium	2	Died p.m.; hypostatic pneumonia
J. D.	72	M	Struck by truck	Fracture of right ilium, right acetabulum and right superior ramus of pubis	45	Improved
J. Mc.	23	M	Fell from truck; wheels ran over him	Fracture of left ischium and left pubis near symphysis	9 AOR	Improved
A. G.	48	F	Fell on street	Fracture of left ischium	7 AOR	Improved
M. F.	35	F	Fell 1 story	Fracture of both rami of right pubic bone; fracture of crest of right ilium into sacroiliac joint	12 AOR	Improved
D. P.	61	F	Fell in kitchen	Fracture of ascending ramus of right pubic bone	20	Improved
V. S.	27	F	Struck by automobile	Fracture of descending ramus of left pubic bone	25	Improved
E. C.	4	F	Struck by taxicab	Oblique fracture of left pubic bone	20	Improved
E. T.	26	F	Fell 2 stories	Oblique fracture of junction of inferior rami of right ischium and pubic bone; fracture of left ilium near upper part of left sacroiliac joint	50	Improved
M. G.	24	F	Jumped from car	Fracture of ascending ramus of right pubic bone	17	Improved
G. C.	11	M	Struck by automobile	Fracture of body of right and left pubic bones and descending ramus of left pubic bone	12	Improved
G. L.	44	F	Struck by automobile	Fracture of left pubic bone; free bone in region of fracture; fracture of right ischium; patient diabetic	52	Improved
A. R.	59	F	Struck by automobile	Fracture of superior rami of both pubic bones and left ilium near sacroiliac joint; patient diabetic	84	Improved
G. Y.	13	F	Fell 1 story (elevator shaft)	Diastatic fracture of right ilium from crest to tip of sacroiliac articulation; widening of symphysis	35	Improved
R. D.	5	M	Struck by truck	Fracture of descending ramus of right pubic bone	57	Improved
E. W.	50	M	Struck by car	Fracture of left acetabulum	35	Improved
P. R.	30	F	Fell 2 stories	Fracture of ascending and descending rami of left pubic bone	27	Improved
O. C.	14	M	Struck by truck	Fracture of superior ramus right pubic bone	16	Improved
E. V.	14	F	Fell 1 story	Fracture of left pubic bone	5	Improved
H. I.	46	M	Struck by car	Fracture of right pubic bone	41	Improved
J. J.	41	M	Fell 1 story	Fracture of right pubic bone near symphysis	15	Improved
H. R.	29	M	Struck by taxicab	Fracture of midportion of body of sacrum and of right ilium	40	Improved
R. D.	26	M	Fell from car	Fracture of inferior ramus of left pubic bone	17	Improved

* In this table and in the following tables, the abbreviation AOR denotes "at own risk."

Table 5.—*Analysis of Cystograms*

Patient	Age	Sex	Cause of Injury	Type of Pelvic Fracture	Cystogram	Urine	Results
1.	23	F	Fell from 3d story	Fracture of right ilium, ascending and descending rami of both pubic bones	Displacement of bladder to left; no evidence of extravasation	Occasional red blood cell	Improved
2.	24	M	Struck by automobile	Fracture of superior ramus of left pubic bone; separation of symphysis pubis	No evidence of vesical injury	No red blood cells	Improved
3. J. H.	11	M	Wagon ran over abdomen	Separation of symphysis pubis	No vesical injury	No red blood cells	Improved
4.	33	M	Fell from fire escape, 4 stories	Multiple fractures of right ilium, extending into sacroiliac joint; fracture of ascending and descending rami of right pubic bone	No vesical injury; incomplete filling of pelvis and calices of right kidney; dilatation of right ureter	Bloody	Improved
5.	30	M	Fell down stairs	Fracture of descending ramus of left pubic bone	Bladder filled normally	No red blood cells	Improved
6.	40	M	Struck by motorcycle	Fracture of body, ascending rami and descending rami of left ischium; fracture of left acetabulum	No vesical injury	Few red blood cells	Improved
7. E. S.	62	M	Fell from wall	Fracture of ascending and descending rami of left pubic bone	Bladder filled normally	No red blood cells	Improved
8.	25	F	Unknown	Fracture of ascending and descending rami of left pubic bone; fracture of right acetabulum; separation of right sacroiliac articulation	Bladder normal	No red blood cells	Improved
9.	23	M	Fell from a truck; wheels ran over him	Fracture of left ischium and left pubic bone near symphysis	Bladder normal	Bloody	Improved
10.	35	M	Fell 1 story	Fracture of both rami of right pubic bone and crest of right ilium into sacroiliac joint	Bladder filled normally	No red blood cells	Improved
11.	13	F	Fell down elevator shaft, 1 story	Diastatic fracture of right ilium from crest to sacroiliac articulation	Bladder filled normally	No red blood cells	Improved
12.	30	F	Fell 2 stories	Fracture of ascending and descending rami of left pubic bone	Compression on left side and hemorrhage	Bloody	Improved
13.	26	M	Fell from car	Fracture of inferior ramus of left pubic bone	No abnormality	Clear	Improved
14.	46	M	Struck by car	Fracture of right pubic bone	No abnormality	Clear	Improved
15.	41	M	Fell 1 story	Fracture of right pubic bone near symphysis	No abnormality	Clear	Improved
16. S. W.	14	M	Run over by truck	Separation of symphysis pubis; separation of right sacroiliac joint; fracture of superior ramus of right pubic bone	Unsuccessful	Frankly bloody	Improved

TABLE 6.—*Vesical and Urethral Injuries*

Patient	Age	Sex	Cause of Pelvic Fracture	Type of Pelvic Fracture	Associated Injuries	Vesical Injuries	Urethral Injuries	Treatment	Time in Hospital	Result
E. B.	23	M	Gunshot	Perforating fracture of left ilium	Perforation of bladder	Yes	No	Laparotomy	4 days	Died of peritonitis
P. B.	33	M	Automobile overturned	Fracture of right pubic bone (superior ramus)	None	None	Yes	Rest in bed	7 days (AOR)	Improved
A. T.	27	M	Struck by automobile	Comminuted fracture of wing of left ilium	Fracture of 11th and 12th ribs posteriorly; fracture of left 8th rib, posterior axillary line; fracture of left ilium	?	? Urine bloody	Rest in bed	3 days	Transferred to Bellevue; traumatic delirium
F. D.	39	M	Fell 5 stories	Fracture of ascending ramus of left pubic bone; fracture of shaft of left femur; fracture of left sacroiliac articulation	Spiral comminuted fracture of upper half of left femur; fracture of transverse processes of 1st and 5th lumbar vertebrae	?	Had bloody urine on admission, was observed for distention and extravasation; condition cleared up	Double Russell traction	24 days	Improved
O. J.	48	F	Struck by taxicab	Fracture of ascending ramus of right pubic bone	Fracture of left femur	Yes	No	Repair of ruptured bladder; def; Russell traction	Still confined (20 days)	Good
W. B.	21	M	Struck by automobile	Fracture of right and left pubic bones; extending into left acetabulum	Abrasions of face, arms and chin; lacerations and contusions of right side of head; subarachnoid hemorrhage; retroperitoneal hemorrhage; rupture of bladder and membranous portion of urethra with laceration of prostate and anterior wall of rectum	Rupture of bladder and urethra		Treatment for shock	11 hr.	Died
S. W.	11	M	Run over by truck	Separation of symphysis pubis; separation of right sacroiliac joint; fracture of right superior ramus of pubis	Rupture of urethra; complete fracture of 4th and 5th lumbar vertebrae	Rupture of bladder and urethra	Na	Conwell sling; suprapubic urethroplasty	3 mo.	Improved
A. B.	27	F	Fell 3 flights	Fracture of pubis on both sides; fracture of acetabulum	Fracture of lower end of right humerus and anterior lip of ulna; rupture of spleen; rupture of fundus of urinary bladder	Rupture of bladder	Na	Laparotomy	6 hr.	Died

catheter in a completely severed uretha an obstruction will be observed to prevent the catheter from passing. If the rupture is partial there may be some difficulty in passing the catheter, but usually, after some difficulty, it can be made to pass.

The bladder may rupture intraperitoneally or extraperitoneally.

Extraperitoneal rupture is usually in the space of Retzius. In this case extravasation may extend upward over the lower anterior portion of the abdominal wall as high as the umbilicus or the back and down behind the rectum. Evidence of irritation and inflammation accompanies the extravasation. Intraperitoneal rupture gives evidence of peritoneal irritation, such as pain, fever and abdominal rigidity. If the

Fig. 1.—Cystogram showing normal conditions.

intra-abdominal extravasation is extensive, a fluid wave is present. An abdominal tap in most instances will confirm the diagnosis. The most important method of diagnosing rupture of the bladder is the taking of a cystogram. Two hundred and fifty cubic centimeters of a 20 per cent solution of hippuran is injected transurethrally through a catheter into the bladder. Immediately thereafter a roentgenogram is taken. If there is a rupture of the bladder the extravasated opaque material will be seen roentgenologically. If the bladder is not ruptured its normal contour will be seen. Intravenous urographic study may be considered by those fearful of introducing infection from without. In eight cases (10.1 per cent) of our series the condition was complicated by vesical or urethral injuries or both.

Table 7.—Pelvic Fracture with Serious Associated Injuries

Patient	Age	Sex	How Injured	Type of Pelvic Injury	Associated Injuries	Time in Hospital	Results
D. R.	18	F	Fell 2 flights from window	Fracture of ascending and descending rami of left pubic bone; incomplete fracture of ilium, above acetabulum	Fracture of bodies of 2d and 3d lumbar vertebrae	90 days	Improved
E. L.	18	M	Struck by truck	Fracture of descending ramus of right pubic bone; fracture into left acetabulum and vertical fracture through sacrum	Fracture of middle third of left clavicle; fracture of right femur, middle of shaft	65 days	Improved; exploratory laparotomy done
F. D.	30	M	Fell 5 stories	Fracture of descending ramus of left pubic bone; dislocation of left sacroiliac articulation	Spiral comminuted fracture of upper half of shaft of left femur; fracture of transverse processes of 1st and 5th lumbar vertebrae	29 days	Improved
S. A.	25	M	Fell from wagon	Fracture of superior ramus of left pubic bone	Fracture of left 7th, 8th, 9th and 10th ribs in posterior axillary line	10 days	Improved
A. C.	51	M	Fell 10 feet	Fracture of external articulating surface of sacrum at right sacroiliac joint; fracture of left acetabulum	Fracture of right transverse process of 5th lumbar vertebra	29 days	Improved
E. W.	?	F	Struck by auto	Fracture of right pubis	Laceration of perineum	37 days	Improved
J. P.	25	F	Fell from 3d story window	Fracture of right ilium, ascending and descending rami of both pubic bones	Fracture of medial intercondyloid spine of right tibia; fracture of 7th, 8th, 9th and 11th ribs on right in axillary line	31 days	Improved
W. P.	21	M	Struck by auto	Fracture of superior ramus of left pubic bone; separation of symphysis	Laceration of right thigh; chip fracture of greater trochanter of left femur	29 days	Improved
M. H.	38	M	Fell 4 stories from fire escape	Fracture of both rami of left pubic bone	Mild intracranial injury and fracture of left radius and ulna	13 days	Improved
A. L.	20	F	Struck by auto	Double fracture of right pubic bone	Multiple fractures of upper right ribs posteriorly	29 days	Improved
J. O.	31	M	Fell from 3d story window	Fracture of left ilium, acetabulum and ascending and descending rami of pubic bone	Fracture of right tibia and fibula, fracture of os calcis and of transverse process of 5th lumbar vertebra	120 days	Improved
I. B.	25	F	Unknown	Fracture of ascending and descending rami of left pubic bone; fracture of right acetabulum; separation of right sacroiliac articulation	Extensive comminuted fracture of lower third of right femur	120 days	Improved
A. A.	46	F	Fell from 3d story window	Fracture of superior rami of both pubic bones	Intracranial injury; fracture of 10th rib on left	19 days	Improved
O. T.	10	M	Fell from 3d story window	Chip fracture of superior rami of right pubic bone	Intracranial injury; epiphyseal separation of left radius	13 days	Improved
H. W.	35	M	Fell from window	Transverse fracture of ascending ramus of left pubic bone	Fracture of left radius and ulna	19 days	Improved
J. B.	15	M	Fell from 2d story window	Fracture of descending ramus of left pubic bone; also of body of left pubic bone; reluxation of left sacroiliac articulation	Fracture of left os calcis, left radius and ulna and left transverse process of 5th lumbar vertebra	17 days	Improved
C. J.	48	F	Struck by taxicab	Fracture of ascending ramus of right pubic bone	Fracture of left femur	60 days	Good
R. A.	33	M	Struck by train	Fracture of crest of left ilium	Traumatic amputation of right leg	157 days	Improved
J. G.	20	M	Fell 3 stories	Fracture of right pubic bone	Pneumothorax; fracture of right internal malleolus; fracture of right rib	55 days	Improved
T. H.	42	M	Fell 12 feet	Fracture of both pubic bones near symphysis	Fracture of left thumb	21 days	Improved
S. W.	11	M	Run over by truck	Separation of symphysis pubis; separation of right sacroiliac joint; fracture of right superior ramus of pubis	Rupture of urethra; compound fracture of 4th and 5th lumbar vertebrae	....	Improved

INVOLVEMENT OF NERVES

A neglected factor in the study of fracture of the pelvis is the question of neural involvement. Although most patients complain of neuralgia, this symptom is only too readily ascribed to the fracture, and no thought is given to possible neural injury. Investigation, however, will frequently reveal neural trauma.

Incidence.—Not much space in the literature is given to discussion of neural injury associated with pelvic fracture. The report of one series gives the incidence as 2 per cent; other figures are as low as 0.75

Fig. 2.—Pelvic fracture which was perfectly reduced by treatment with the Conwell sling.

per cent. The incidence of neural involvement in one series, in which neural injuries were particularly watched for, was 9 per cent.

Site of Fracture.—Neural injuries occur most frequently with fractures of the posterior rim of the pelvis. One must not forget that a sacroiliac joint may have been luxated at the time of the injury and yet not show such an injury on the roentgenogram, as it may have sprung back in place so that the roentgenogram shows only the anterior ring affected.

Nerves Involved.—Nerves frequently affected are: (1) the lumbo-sacral cord at the pelvic brim, (2) the sciatic nerve, especially the pero-

neal component, and (3) the obturator nerve (in fracture of the anterior ring). The sciatic nerve arises from the main band of the sacral plexus. It splits in the thigh into the common peroneal and the tibial nerve. The sacral plexus is composed of the lumbosacral trunk, the anterior division of the first sacral nerve and portions of the anterior

Fig. 3.—*A*, acetabular fracture of patient E. W. (table 4). *B*, same fracture after treatment with Russell traction.

divisions of the second and the third sacral nerve. The lumbosacral trunk is composed of the anterior division of the fifth lumbar nerve and a part of the anterior division of the fourth lumbar nerve. The femoral nerve is composed of dorsal divisions of the second, the third and the fourth lumbar nerve.

Symptoms.—Neural injury causes disturbance of reflexes, motor function and sensation. Neuralgia is a common result. Disturbances of sensation are not uncommon, especially when the lateral cutaneous femoral nerve is involved. This nerve supplies the upper lateral aspects of the thigh and arises from the dorsal divisions of the second and the third lumbar nerve.
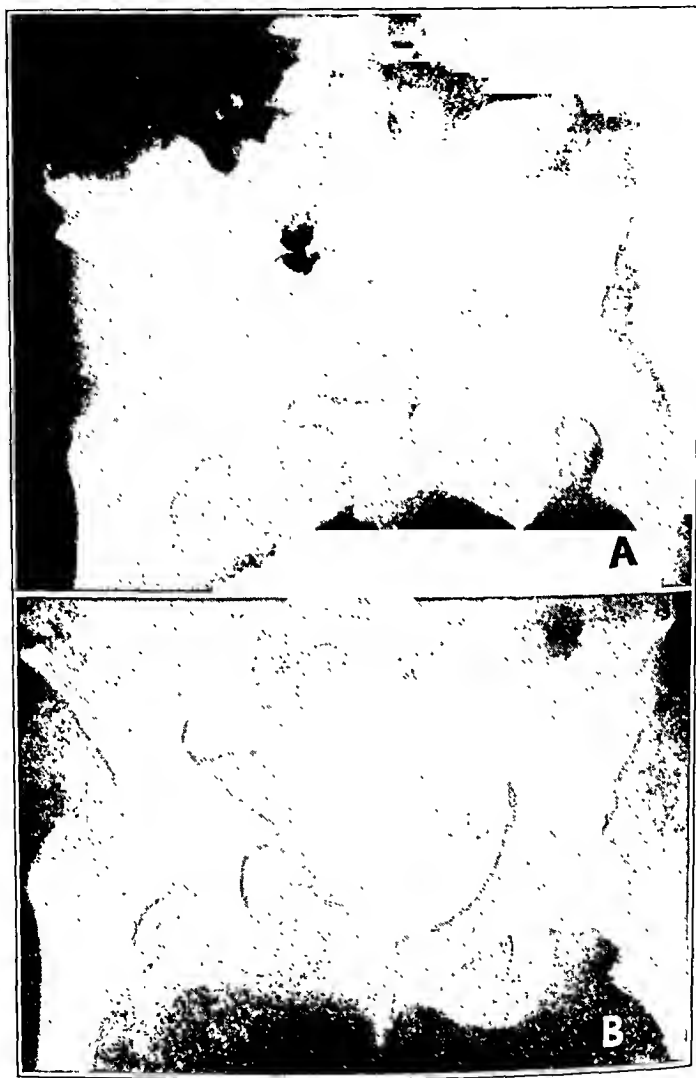
Fig. 4.—*A*, roentgenogram showing the pelvic fracture of patient (table 5). *B*, cystogram of the same patient.

When the lumbosacral plexus is involved the common symptoms are weakness of flexion of the toes, weakness of the muscles of the calf and weakness of the anterior tibial muscle. Involvement of the sacral plexus causes weakness of the muscles of the thigh, neuralgia and muscle atrophy. Involvement of the peroneal nerve gives the symptom of foot drop. Application of hot water bottles often causes burns in an anesthetic area.

Treatment.—The condition is treated with dry heat, diathermy, braces or a splint (for foot drop), and a cradle to relieve pressure from bed clothes.

End Results.—Spontaneous regeneration frequently occurs. Neuralgia and muscular weakness are the two outstanding sequelae.

Conclusion.—In every case of fracture of the pelvis careful neurologic examination is indicated to insure early institution of proper treatment.

TREATMENT OF PELVIC FRACTURE

In the main, our treatment for pelvic fracture has been simple. The uncomplicated fracture requires little more than strapping or rest in

Fig. 5.—Roentgenogram of the pelvic fracture of patient 4 (table 5).

bed. Several of our patients with separation of either the symphysis pubis or the sacroiliac joint have done exceedingly well with the suspension sling recommended by Noland and Conwell. Our results in these cases have been eminently satisfactory. When there is marked upward or downward displacement of the fragments, as in the Malgaigne type of fracture or in a fracture of the acetabulum, we have used Russell traction applied to the affected side. We recommend this especially for acetabular fracture, results being exceptionally good. Russell traction, however, should not be used if there is renal infection as indicated by the presence of pus in the urine and elevation of temperature, for the position of the body with the foot of the bed elevated is not

conducive to drainage of the kidneys. In all cases in our service cystograms are now taken as a routine. This enables us to diagnose a rupture of the bladder while there are still extremely few clinical manifestations. In the presence of vesical injury immediate laparotomy is performed. In the presence of urethral injury our first concern is that there shall be no extravasation of urine. Further operative procedures then depend
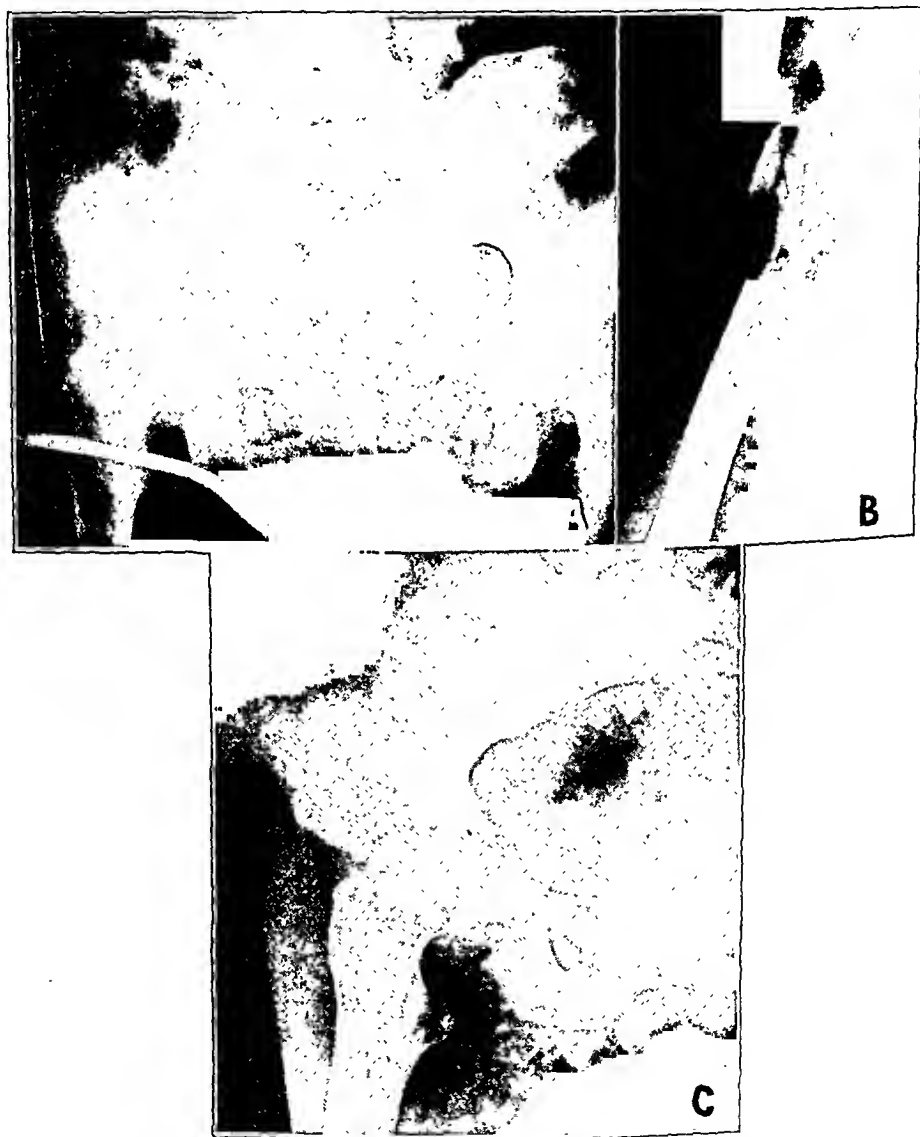
Fig. 6.—Roentgenograms in the case of patient I. B. (table 7). *A*, fracture of the acetabulum. *B*, fracture of the femur. *C*, roentgenogram taken after treatment with Russell traction.

on the patient's general condition. With proper drainage the repair of the urethra may be delayed until the patient has recovered from shock and is able to withstand operation. Shock itself is combated in the usual manner by the use of warm blankets, morphine, venoclysis and other procedures for relief of symptoms.

REVIEW OF LITERATURE

In the following pages we shall give a "highlight review" of the treatment of fractures of the pelvis for the past ten years.

Noland and Conwell [2] report 125 cases, with a mortality of 16 per cent. They describe in detail the overhead pelvic suspension frame. Their usual procedure is traction and suspension for about forty-two days, followed by application of a pelvic belt. They report operative intervention to replace fragments in 2 cases. In 1933, the same authors [3] reported 60 new cases in addition to the previous 125. The mortality for the entire 185 cases was 16.2 per cent : 19 patients died within twenty-four hours. The average stay in the hospital was fifty-three days, and the ratio of male to female patients was 3 to 1. The authors used their customary treatment with the pelvic suspension frame, traction being applied on both lower extremities with abduction of 15 to 20 degrees. They emphasize the use of the spreader to prevent too great a lateral pressure. They use roentgen evidence of callus formation to determine the time at which weight bearing may be permitted. Noland [4] advocates painstaking examination, minimal handling, examination by means of a portable x-ray apparatus and, if necessary, catheterization to obtain a specimen of urine. He advocated waiting several hours before injecting opaque fluids to determine whether the bladder is intact. (It has not been our custom to wait.) His method involves suspension by a canvas sling from the upper third of the thigh to the lower dorsal region. Countersuspension depends on the weight of the parts supported. Suspension is supplemented in every case by traction on the legs and thighs. No traction is used for fracture of the anterior superior or the inferior spine, but simply suspension plus flexion at the knees by means of a pillow. The wooden spreader is also used except when there is separation of the symphysis pubis. In ordinary cases this treatment is continued for forty-two days. The apparatus is removed and a belt applied ; the patient is then allowed to remain in bed one more week. He is out of bed by the seventh or eighth week and is allowed to bear weight, using crutches. Hot tub baths and local heat, electrotherapy, hydrotherapy and massage are used during this time. Noland makes the important note that while anatomic position was good in only 55 per cent, functional results were good in most cases.

Koster and Kasman [5] describe an apparatus devised by them, which they have used in 14 cases. Its special recommendation is that the patient

2. Noland, P. L., and Conwell, H. E.: Acute Fractures of the Pelvis. J. A. M. A. 94:174 (Jan. 18) 1930.

3. Noland, L., and Conwell, H. E.: Fractures of the Pelvis, Surg., Gynec. & Obst. 56:522 (Feb.) 1933.

4. Noland, L.: Fractures of the Pelvis, Am. J. Surg. 38:608 (Dec.) 1937.

5. Koster, H., and Kasman, L. P.: Treatment of Fractures of the Pelvis, J. Bone & Joint Surg. 19:1130 (Oct.) 1937.

is immediately relieved of pain on motion. This apparatus is used for fracture involving the pelvic girdle in which displacement is to be corrected. These authors state, however, that if the displacement can be corrected by traction this should also be applied. (We have not felt it necessary to use this specially devised apparatus.)

Rankin [6] reports 449 cases. He recommends that the treatment be fitted to each individual case, the treatment recommended in the majority of cases being extension of the lower extremities with some form of pelvic sling. He is a strong advocate of immediately using the various forms of physical therapy, concluding that if used early such measures shorten the period of hospitalization.

Kreuscher [7] reports 185 cases. Essentials of his treatment are complete relaxation on a Bradford frame, traction on the lower extremities and overhead suspension. He states that open operation is rarely indicated and that he does not care for the circular plaster cast but immobilizes his patients for six to ten weeks. (We have never found it necessary to use the Bradford frame nor traction on both lower extremities. We, also, have had no use for the circular cast.)

Cubbins' [8] experience has been that the average fracture of the pelvic ring involving the rami of the pubis and ischium with little or no displacement will return to perfect form and function in about twelve weeks, five to seven weeks being spent by the patient in bed without any particular dressing; the patient may be "up and around" under treatment for the succeeding three to five weeks. With wide separation, the patient is suspended in a sling. Moleskin adhesive tape may be used below the iliac crest and over the greater trochanters. The patient may also be suspended in a hammock attached to a Balkan frame. Supports of this hammock may be crossed to give greater lateral pressure. For upward dislocation of one side of the pelvis, traction of 50 to 75 pounds (22 to 34 kg.) on the well limb is applied, with counterpull by means of a belt beneath the opposite tuberosity of the ischium. If this is not successful, Cubbins suggested the use of the Hawley table with extension by screw traction. For acetabular fracture he uses lateral traction with a band around the thigh in addition to longitudinal traction. In some cases he has used a large screw driven into the neck of the femur, lateral traction being applied to this. For fracture of the acetabulum in which the fragments are locked he does an open operation to extract the head of the femur.

6. Rankin, L. M.: Fractures of the Pelvis, Ann. Surg. **106**:*266* (Aug.) 1937.

7. Kreuscher, P. H.: Fractures of the Pelvis, Indust. Med. **5**:*185* (April) 1936.

8. Cubbins, W. R.: Fractures of the Pelvis, Northwest Med. **35**:*63* (Feb.) 1936.

Billington[9] in his cases of simple fracture orders rest in bed with an adhesive plaster swathe. He also uses a pelvic binder of elastic stockinet held in place by perineal straps. For more severe fracture the pelvic hammock and bilateral leg traction, as described by Conwell, are used.

Weil, Henry and Rusbridge[10] report 228 cases. They give an excellent exposition of the initial treatment of this type of fracture and stress the treatment of the injured bladder. They insist that rectal examination must not be overlooked. They like the hammock suspension of Conwell. Their patients are usually confined to bed for eight to ten weeks. In their series of cases the mortality was 12.2 per cent, and the period of disability averaged one hundred and forty-eight and two-tenths days.

Langan[11] reports 40 cases and describes the use of the Jones splint. (We have never had recourse to the use of this splint.) Langan manipulates the fragments through the vagina and rectum. (This has never been done in any of our cases.) However, in the article referred to Langan does not distinguish between the sites of fractures of the neck of the femur, and it is therefore hard to evaluate the value of the splint from the evidence presented.

Haggart[12] uses the pelvic swathe for fracture complicated by visceral injuries. His method closely follows that of Conwell. In an occasional case he uses plaster boots applied to both legs and connected by a cross member. (This method has never been used by us.)

Papik[13] advocates the use of a Jones and Anderson splint to obtain simultaneous traction and abduction for central dislocation of the head of the femur. The legs must be placed in a cast in which the apparatus is incorporated. (This method has never been necessary in our cases. We feel that Russell traction is more effective and more comfortable.)

McBride[14] describes an apparatus for traction and fixation which allows the patient to be raised and lowered without disturbing the traction. (Again, we have felt that Russell traction answers the purpose very well.)

9. Billington, R. W.: Fractures of the Pelvis, J. Tennessee M. A. **28**:453 (Nov.) 1935.

10. Weil, G. C.; Henry, J. P., and Rusbridge, H. W.: Treatment of Fractures of the Pelvis, Pennsylvania M. J. **38**:942 (Sept.) 1935.

11. Langan, A. J.: Use of the Jones Splint in Treatment of Fractures of the Pelvis, J. Bone & Joint Surg. **17**:435 (April) 1935.

12. Haggart, G. E.: Fractures of the Pelvis, S. Clin. North America **14**:1197 (Oct.) 1934.

13. Papik, C.: The Management of Pelvic Fractures, Internat. J. Med. & Surg. **47**:78 (Feb.) 1934.

14. McBride, E.: The Underslung Traction Saddle Frame in Fractures of the Pelvis, Ann. Surg. **97**:309 (Feb.) 1933.

Henson and Lublin [15] report 112 cases. Their patients are strapped tightly with adhesive tape. Traction is not used. Plaster casts have been used in 12 per cent of the cases. The average stay in the hospital is twenty-three and one-half days. No attempt is made to obtain perfect anatomic position.

Gilmour [16] cites 81 cases. In his article he lays particular stress on the diagnosis of rupture of the bladder.

Leadbetter [17] reports 100 cases, 80 per cent of the patients being female. His method of treatment is related to the suspension and traction apparatus, including use of the Balkan frame, the Thomas splint and fixation with adhesive tape. When the fragments do not move in forty-eight hours he uses skeletal traction by pins or tongs. (We have never found it necessary to do this.) Traction is maintained in his cases for six weeks, and weight bearing is allowed at the tenth week. Open operation is performed only for overriding fracture of the pelvic bones. In a discussion of his article much is made of the Maxwell-Ruth lateral traction method, which we have never found necessary.

Rutherford [18] reports about 200 cases without a fatality. His patients are placed on a level traction bed and allowed to move about. He rarely uses traction or a plaster cast.

Jones and Buckner [19] report 40 personal cases and 312 other cases. The mortality in the former series was 2.5 per cent and in the latter 15 per cent. For fractures of the iliac wing they use a well fitting body cast. For fracture involving the acetabulum they have used the Whitman spica with 20 per cent abduction of the leg, allowing the cast to remain in place for twelve weeks. Forward displacement of half the pelvis is treated by skeletal traction by means of ice tongs applied just above the condyles of the femur. When there is lateral spreading they use suspension with a wide canvas band, the suspending ropes being crossed. For separation of the symphysis pubis they perform a wiring operation. (The last named we have not needed, as the pelvic sling produces the desired results.)

Martin [20] describes a belt which he has used in 5 cases, with satisfactory results.

15. Henson, E. B., and Lublin, R. D.: Fractures of the Pelvis, West Virginia M. J. **28**:539 (Dec.) 1932.

16. Gilmour, W. R.: Acute Fractures of the Pelvis, Ann. Surg. **95**:161 (Feb.) 1932.

17. Leadbetter, G. W.: Fractures of the Pelvis, South. M. J. **25**:742 (July) 1932.

18. Rutherford, A. G.: Management of Fractures of the Pelvis, West Virginia M. J. **27**:298 (July) 1931.

19. Jones, E. O., and Buckner, H. T.: Fractures of the Pelvis, Northwest Med. **30**:269 (June) 1931.

20. Martin, E. D.: A New Bandage for Treatment of Fractures of the Pelvis, New Orleans M. & S. J. **83**:678 (April) 1931.

Todd [21] reports 47 cases, with 3 deaths. He advises the use of a Bradford frame, with strapping or a binder about the pelvis. This is then replaced with a light plaster cast. The patient is kept in bed one month. He cites a case in which he used heavy traction and suspension. Michel [22] uses the Bradford frame with the knee flexed on a pillow and a broad encircling band of adhesive tape around the pelvis. When conditions indicate it he also uses pelvic suspension with a spreader and traction on the lower extremities.

Parker [23] cites 19 pelvic fractures with a mortality of a little more than 10 per cent. In most cases he uses simple rest in bed with the patient flat on the back, sand bags providing support for the legs and pelvis. In case of displacement he uses traction and abduction. For fracture of the acetabulum he formerly used traction followed by application of a plaster cast. This was found unsatisfactory, and he now uses the overhead frame with suspension and extension. His article contains a good discussion of vesical and renal injuries.

Brooksher [24] reports 25 cases, with a mortality of 12 per cent. In the majority of his cases he has used strapping with adhesive plaster. He has also used Buck's extension plaster cast and the Bradford frame. Open operation is not performed.

Herzikoff [25] describes an apparatus which uses the sling and suspension for fracture of the pelvis with wide separation of fragments, especially in the region of the symphysis pubis. He condemns the swathe, the plaster spica, the Bradford frame and the Thomas splint.

McNealy and Willems [26] report 30 cases, the average period of hospitalization being ninety-five days. For forward displacement they use an extension apparatus. For pubic fracture with overriding they manipulate the fragments vaginally or rectally. They also use a plaster of paris cast extending from the umbilicus to the midthigh, putting a cross bar between. For disturbance of the acetabulum they use the Whitman method and the method of Putti, which is the insertion of a steel pin through the trochanter and the application of traction. (It has never

21. Todd, M. H.: Fractures of the Pelvis, Virginia M. Monthly **57**:781 (March) 1931.

22. Michel, H. M.: Fractures of the Pelvis, South. M. J. **24**:263 (March) 1931.

23. Parker, O. W.: Fractures of the Pelvis, Minnesota Med. **14**:29 (Jan.) 1931.

24. Brooksher, W. R.: Fractures of the Pelvis, J. Arkansas M. Soc. **26**:242 (May) 1930.

25. Herzikoff, S.: Apparatus Used in Treatment of Fractures of the Pelvis, California & West. Med. **32**:253 (April) 1930.

26. McNealy, R. W., and Willems, J. D.: Fractures of the Pelvis, Am. J. Surg. **8**:573 (March) 1930.

been our policy to manipulate fragments either rectally or vaginally or to use the Whitman spica.)

Colp and Findlay [27] review 35 cases. Practically the only treatment which they render is rest in bed for about thirty days. The patient is allowed to walk on about the thirty-eighth day. They have also used pelvic strapping and elastic belts. They report 1 case of unsuccessful treatment with the Balkan frame and traction to bring down a posterior displacement of the ilium. They do not resort to operation or to casts.

Boorstein [28] reports on 100 cases. His favorite method is to use the Bradford frame, with strapping adhesive plaster and lacing in front. For upward displacement he applies extension of both limbs by weights and pulleys or by the Thomas Jones brace.

Bates [29] remarks that the two essentials of treatment are reduction and immobilization. For a broken iliac crest or ramus he uses replacement by pressure or manipulation and retention by pads and adhesive tape. For simple fracture with intrapelvic damage, extension of both lower limbs with abduction of the hips and elevation of the foot of the bed are used. For pelvic fracture associated with fracture of the thigh he uses the Hodgen splint. He discusses in detail the Murphy sling for the handling of any type of pelvic fracture.

Wakeley [30] reports 100 cases. For fracture of the whole pelvic girdle (44 cases reported) he uses a broad binder for ten days and then a cast for six weeks. The patient is allowed to be up on crutches in nine weeks. For fracture of the ilium (18 cases reported), the os pubis (24 cases reported) and the sacrum (4 cases reported) the treatment is the same. For fractures of the ischium (5 cases reported) therapy consists of rest in bed for six weeks. For fracture of the acetabulum (2 cases reported) extension is used for two weeks, followed by immobilization in plaster for six weeks. For fracture of the coccyx (3 cases reported) he manipulates the fragments through the rectum and prescribes rest in bed.

Holderman [31] discusses only pelvic fracture with separation of the symphysis pubis. He does not use the swathe or strapping with adhe-

27. Colp, R., and Findlay, R. T.: Fractures of the Pelvis, Surg., Gynec. & Obst. 49:847 (Dec.) 1929.

28. Boorstein, S. W.: Fractures of the True Pelvic Ring, Am. J. Surg. 7: 633 (Nov.) 1929.

29. Bates, T. H.: Fractures of the Pelvis: Treatment by Murphy Sling, J Florida M. A. 16:68 (Aug.) 1929.

30. Wakeley, C. P. G.: Fractures of the Pelvis, Brit. J. Surg. 17:22 (July) 1929.

31. Holderman, H. H.: Fractures of the Pelvis with Separation of the Symphysis Pubis, Pennsylvania M. J. 32:16 (Oct.) 1928.

sive tape. However, he does describe a belt with a buckle, which is passed over and around the pelvis with the patient on a Bradford frame.

Sever [32] reports 51 cases, with 1 death. This article contains a good review of the literature. He concludes that acetabular fracture is the most disabling and advises that the Whitman abduction method or the method of Putti [33] be used. For fracture of the ilium or pubic arch he uses rest in bed with a tight swathe. Occasionally he makes use of a pelvic sling. For fracture of the pubic arch, the sacroiliac joint and the wing of the ilium, with displacement, he makes use of traction on the leg combined with a pelvic swathe.

Wilson [34] competently discusses vesical and urethral injuries. He applies a plaster cast for the pelvis and both thighs, leaving this in place for two to three months. No weight bearing is permitted for one month after the cast is removed. He advocates the use of silver wire to bring together separated pubic bones. For acetabular fracture he immobilizes the joint in plaster for two months, with moderate abduction of the thigh. When the head of the femur is driven through the acetabulum he uses a hook above the greater trochanter with manipulation through the vagina or rectum to replace the fragments and then immobilizes the pelvis in plaster with full abduction.

Furniss [35] reports 20 cases with good results irrespective of the treatment employed. He uses on occasion rest in bed, a girdle of adhesive tape 2 inches (5.08 cm.) wide or sand bags to the outer side of the thighs. He also uses manual reposition of the fragments. He commends suspension and traction.

(An apparatus has recently been described; it is called the Brendel symphysis reduction tractor. By means of two hooks inserted into each obturator foramen, the separated symphysis may be brought together and wired. The tractor is then removed. We have had no experience with this apparatus.)

ANALYSIS OF DEATHS

There were 14 deaths in our series of 79 cases, a percentage of 17.7 per cent. Nine patients died within six hours. Following is a brief report of the cases in which death occurred. The patients in cases 1 to

32. Sever, J. W.: Fracture of the Pelvis, New England J. Med. **199**:16 (July 5) 1928.

33. Putti, V.: Sulla terapia della lussazione centrale del femore, Chir. d. org. di movimento **11**:530 (Aug.) 1927.

34. Wilson, G. E.: Fractures of the Pelvis, St. Michael's Hosp. M. Bull. **3**:56 (Dec.) 1927.

35. Furniss, J. N.: Fractures of the Pelvis, Internat. J. Med. & Surg. **40**: 344 (Aug.) 1927.

5, inclusive, lived over six hours after injury; those in cases 6 to 14, inclusive, died within six hours.

Case 1.—E. B., a man aged 23, had a gunshot wound in the pelvic region. Roentgen examination revealed a perforating fracture of the left ilium, the ascending ramus of the left pubic bone and the sacrum near the sacroiliac articulation. The bladder was also perforated. Operation was performed immediately to close the vesical perforations. Peritonitis developed, and the patient died four days later.

Case 2.—J. J., a man aged 25, fell down a flight of ten steps. The right ilium was fractured, with no associated injury. The patient died on the third day. The postmortem diagnosis was fracture of the pelvis and hypostatic pneumonia.

Case 3.—H. J., a man aged 58, jumped from a third story window. He received a fracture of the lateral mass on the left side of the sacrum and a fracture of the descending ramus of the left pubic bone. He also had fractures of the transverse processes of the fourth and fifth lumbar vertebrae. Infection of the urinary tract developed, and the patient died fourteen days later. He was not catheterized during his stay in the hospital.

Case 4.—J. J., a woman aged 28, jumped four stories from a window. Roentgenograms showed comminuted fractures of the ascending and descending rami, the right pubic bone, the right acetabulum and the right ilium. There were associated injuries, consisting of the following: fracture of the right transverse processes of the fifth lumbar vertebra; fracture of the coccyx; fracture of the tibia and the fibula, and fracture of several metacarpal bones. This patient survived for sixty-two hours.

Case 5.—W. B., a man aged 24, was struck by an automobile. The pelvis showed fractures of the right and the left pubic bone, extending into the left acetabulum. In association with these there were subarachnoid hemorrhage, rupture of the bladder and the membranous portion of the urethra and laceration of the prostate and the anterior wall of the rectum. This patient lived eleven hours and was reported by the medical examiner as having died of shock and retroperitoneal hemorrhage.

Case 6.—F. M., a man aged 28, was found lying in the street. The cause of the pelvic fracture was unknown. Fracture of the left ilium, the left acetabulum and the decending ramus of the left pubic bone was present. In addition, there were fractures of the left femur, the right femur and the right humerus. There was also an intracranial injury. The patient died four hours after his admission to the hospital. The postmortem diagnosis was multiple fracture associated with laceration of the liver.

Case 7.—R. T., a man aged 26, jumped from a window. Roentgen examination revealed a separation of the symphysis pubis and a compound fracture of the right ankle. The patient lived one hour. The postmortem diagnosis was fractures of the pelvis and the right leg, with shock.

Case 8.—C. V., a boy aged 15, was caught between two "L" cars. There were fracture of the descending ramus of the right pubic bone and also fracture of right radius, the right ulna, the right femur and the right tibia. The patient lived six hours. The postmortem report corresponded with the clinical findings.

Case 9.—An unidentified Negro had a fracture of the ascending and descending rami of the left pubic bone and the outer part of the left side of the sacrum, near the acetabulum. He also had a comminuted fracture of the upper third of the

Table 8.—*Analysis of Deaths*

Patient	Age	Sex	Cause of Pelvic Fracture	Type of Injury	Associated Injuries	Time in Hospital	Cause of Death
E. B.	23	M	Gunshot	Perforating fracture of left ilium, left ascending ramus of puble bone and sacrum near left sacroiliac articulation	Perforation of bladder	4 days	Peritonitis
J. J.	25	M	Fell 10 steps	Fracture of right ilium	None	5 days	Postmortem diagnosis, fracture of pelvis; hypostatic pneumonia
H. H.	53	M	Jumped from 3d story window	Fracture of internal mass of left side of sacrum and descending ramus of left puble bone	Fracture of transverse process of 4th and 5th lumbar vertebrae	14 days	Infection of urinary tract
F. M.	28	M	Unknown	Fracture of left ilium, left acetabulum, descending ramus of right puble bone	Fracture of left femur, right femur, right humerus; intracranial injury	4 hr.	Multiple fractures; lacerations of liver
R. T.	20	M	Jumped from window	Separation of symphysis pubis	Compound fracture of right ankle	1 hr.	Postmortem diagnosis, fracture of pelvis and right leg; shock
C. V.	16	M	Caught between "L" cars	Fracture of descending ramus of right puble bone	Fracture of right radius, right ulna, right femur and right tibia	6 hr.	Postmortem diagnosis same as clinical findings
U. C. M.	?	M	Unknown	Fracture of ascending and descending ramus of left puble bone and outer part of left side of sacrum, near acetabulum	Comminuted fracture of left femur, extending into intertrochanteric region	1½ hr.	Multiple fractures; shock
U. C. M.	22	M	Fell from window	Multiple fractures of pelvis	Multiple fractures of long bones	5 min.	Multiple fractures; shock
L. R.	20	M	Jumped 5 stories	Compression fracture of sacrum and dislocation of both sacroiliac joints	Fracture of 12th dorsal and 1st lumbar vertebral bodies; fracture of transverse process of 5th lumbar vertebra	2 hr. 10 min.	Shock; internal injuries; multiple fractures
E. J.	27	M	Fell from 3d story window	Fracture of body of right puble bone	Fracture of skull; laceration of brain; fractures of 5th to 9th right ribs; laceration of right kidney; puncture of chest and heart	4 hr. 25 min.	Postmortem diagnosis same as clinical findings
J. J.	28	F	Jumped 4 stories	Comminuted fracture of ascending and descending rami of right puble bone; fracture of acetabulum; fracture of right ilium	Fracture of transverse process of right and left 5th lumbar vertebrae; fracture of coccyx; fracture of tibia and fibula	12 hr.	Died
W. B.	21	M	Struck by automobile	Fracture of right and left acetabulum	Shock; retroperitoneal hemorrhage; ruptured bladder	11 hr.	Died
B. H.	43	M	Unknown	Fracture of crest of left ilium	Fracture of spinous process down dorsolumbar portion of spine	3 hr.	Died
A. B.	27	F	Fell 3 stories	Fracture of puble bones; fracture of acetabulum	Fracture of lower end of right humerus and of right ulna; injury to bladder and spleen	6 hr.	Died

left femur, extending into the intertrochanteric region. The patient lived one and one-half hours. The cause of death was reported as multiple fractures and shock.

CASE 10.—An unidentified Negro aged 32 was admitted to the hospital after falling from a window. There were multiple fractures of the pelvis and multiple fractures of the long bones. The patient lived five minutes. The cause of death was reported as multiple fractures and shock.

CASE 11.—L. R., a man aged 20, jumped from the fifth story of a house. A compression fracture of the sacrum and dislocation of both sacroiliac joints occurred. There were also fractures of the bodies of the twelfth dorsal and the first lumbar vertebra and a fracture of the right transverse process of the fifth lumbar vertebra. The patient lived two hours and ten minutes. The cause of death was reported as multiple fractures, and shock.

CASE 12.—E. J., a man aged 27, fell from a third story window. The body of the right pubic bone was fractured. There were also fracture of the skull with laceration of the brain, fractures of two to nine right ribs and lacerations of the right kidney. The postmortem report corresponded with the clinical findings.

CASE 13.—B. H., a man aged 43, was injured in an unknown manner. The pelvic fracture consisted of a fracture of the crest of the left ilium. The associated injuries included fractures of the spinous processes of the lower dorsal, the lumbar and the sacral vertebrae. The cause of death as reported by the medical examiner was fracture of the pelvis and retroperitoneal hemorrhage. The man lived three hours.

CASE 14.—A. B., a woman aged 27, fell three stories from a window. Bilateral fracture of the pubic bone into the right acetabulum occurred. In addition, there were fractures of the right humerus and ulna, rupture of the spleen and rupture of the bladder. The patient lived six hours.

SUMMARY AND CONCLUSIONS

1. Cystograms are of inestimable value in the diagnosis and treatment of pelvic fractures and associated conditions.

2. A simple method of treatment is preferable to a complicated procedure.

3. Treatment should never be a matter of routine but should be adopted to each case.

4. Concomitant pathologic conditions of the genitourinary tract must be carefully searched for.

5. Neurologic examinations must be made in every case.

6. Pelvic fracture with associated injuries is not infrequent. The latter must be constantly sought for.

FATAL PULMONARY EMBOLISM

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The frequency of sudden death from massive pulmonary embolism in the patient who has successfully passed through a major surgical operation or is recuperating from an injury, the recent parturient and the person with cardiac disease or phlebitis warrants a consideration of this condition.

The incidence of fatal pulmonary embolism may be seen from the following figures:

			Percentage
Belt [1] (Toronto)	767 autopsies (med. : surg. :: 40 : 16)		6.5
McCartney [2] (Minnesota)	14,419 autopsies 9,615 medical deaths 2,122 traumatic deaths 2,351 postoperative deaths 231 postpartum deaths	(1.82%) (3.57%) (5.10%) (5.25%)	2.72
Collins [3] (Los Angeles).................... ..	10,940 autopsies		2.07
Russum and Kemp (Omaha)................	1,781 autopsies		1.31
Yearly deaths in United States............	33,748 (Barnes [4])		
Persons alive now who will die of embolism, 3,068,000 (Barnes [4])			

In our own small series, the basis of this communication, 5 deaths were post-traumatic, 5 followed medical treatment, 13 were postoperative and 1 was postpartum. The cases were observed in 1,781 consecutive unselected autopsies on adults from Jan. 1, 1926, to Oct. 31, 1937. The material came from general hospitals and from the coroner's service.

A study of our own material and a survey of the literature indicate the importance of the following three points:

1. The increased risk of this complication for certain persons and with certain types of operation.

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1. Belt, T. H.: Thrombosis and Pulmonary Embolism, Am. J. Path. **10**:129-144 (Jan.) 1934.

2. McCartney, J. S., cited by Barnes.[4]

3. Collins, D. C.: Pulmonary Embolism Based upon a Study of Two Hundred and Seventy-One Instances, Am. J. Surg. **33**:210-219 (Aug.) 1936.

4. Barnes, A. R.: Pulmonary Embolism, J. A. M. A. **109**:1347-1353 (Oct. 23) 1937.

2. The advantage of recognizing nonfatal pulmonary embolism and the premonitory signs of fatal embolism.

3. The possibility of preventing the condition and of emergency surgical intervention when embolism has occurred and death is not immediate.

APPRECIATION OF RISK OF EMBOLISM

The influence of age, sex, type of operation, cardiac disease and obesity must be considered for individual patients.

Age.—Age is a predisposing factor. In our series the youngest patient was 34 and the oldest 68. Barker [5] reviewed the deaths at the Mayo Clinic following surgical operations from 1928 to 1933 and found that in the cases in which autopsy was done 93 per cent of embolisms were in persons over 40 years of age and 70 per cent in those over 50. Robertson [6] stated that the clinical histories in such cases are similar in that the age incidence is over 30 years. Vance,[7] in 60 deaths from embolism following trauma, found an age incidence of 30 to 80, with an average of 55. Henderson [8] in 1927 reviewed the autopsy records of the Mayo Clinic for the preceding ten years and found the average age at death from pulmonary embolism to be 53.2, which is 10.4 years greater than the average age of patients operated on there. These figures indicate that the danger of embolism is slight before the age of 30 and increases sharply after 40.

Cardiac Disease.—In 13 of our 24 cases some type of cardiac disease was demonstrated at autopsy. In all of our medical cases the heart was damaged.

In various series of fatal embolisms cardiac disease has a high incidence. In Belt's [1] cases 84 per cent of patients had impaired cardiac function.

The age distribution and cardiac involvement in our series was as follows:

31-40	5 cases	(2 postoperative, 3 medical)
		Cardiac involvement—2 medical.
41-50	9 cases	(6 postoperative; 1 medical; 1 traumatic; 1 puerperal)
		Cardiac involvement—2 postoperative; 1 medical.
51-60	5 cases	(3 traumatic; 1 medical; 1 postoperative)
		Cardiac involvement—1 medical; 1 traumatic; 1 postoperative.
61-70	5 cases	(4 postoperative; 1 traumatic)
		Cardiac involvement—all cases.

5. Barker, N. W., cited by Barnes.[4]

6. Robertson, H. E.: Pulmonary Embolism Following Surgical Operation, Am. J. Surg. **26**:15-18 (Sept.) 1934.

7. Vance, B. M.: Thrombosis of the Veins of the Lower Extremity and Pulmonary Embolism as a Complication of Trauma, Am. J. Surg. **26**:19-26 (Oct.) 1934.

8. Henderson, E. F.: Fatal Pulmonary Embolism: A Statistical Review, Arch. Surg. **15**:231-236 (Aug.) 1927.

Sex.—The incidence of embolism is somewhat higher in the female sex, according to most writers. In our cases the sex distribution is the reverse of that encountered in any large series, as 15 of our patients were men and 9 were women. Henderson found death due to embolism in 223 patients, 104 men and 119 women. In Vance's 60 cases of post-traumatic embolism there were 37 female and 23 male patients. In 1927 McCartney[9] examined 9,225 necropsy records at the University of Minnesota and noted 73 deaths due to embolism, occurring in 40 males and 33 females. He stated that sex plays no important role. Later the same author[10] made an additional study of the autopsies from 1927 to 1933 and observed a significant difference in the incidence of embolism after trauma in the male and in the female. In the male it was 2.8 per cent and in the female 8.6 per cent. Differences in age did not explain the variation, while the incidence of coincident cardiac disease was even higher in males. Although unable to demonstrate the fact in his cases, McCartney suggested that probably the higher incidence of varicose veins in women explains the greater incidence of embolism.

Type of Operation.—Consideration of the type of operation is most important in estimating the danger of embolism in surgical cases. In our series the incidence was as follows: prostatectomy, 3; varicose vein resection, 1; gastroenterostomy, 1; cholecystectomy, 1; herniotomy, 3; hysterectomy and appendectomy, 1; resection of rectum, 1; appendectomy, 1; salpingo-oophorectomy, 1, and thoracotomy, 1.

Barker[5] reported the frequency of postoperative embolism at the Mayo Clinic for the period from 1928 to 1933 greatest after the following operations, in descending order of frequency: exploratory laparotomy for inoperable malignant tumor, colostomy, enterostomy, femoral or inguinal herniotomy, resection of the intestine, hysterectomy, operation for ruptured appendix, operations on the prostate and urinary bladder, open reduction of fracture, operations on the brain and the spinal cord and cholecystectomy.

Most postoperative emboli are preceded by abdominal operations. Numerous studies are available in this connection. Henderson found only 43 cases of fatal embolism following extra-abdominal operations. In the group were 14 operations for hernia and 8 operations on the breast.

Embolism after operations on the abdomen or the pelvis seems to result from interference with the circulation in the lower extremities,

9. McCartney, J. S.: Pulmonary Embolism, Arch. Path. **3**:921-937 (June) 1927.

10. McCartney, J. S.: Pulmonary Embolism Following Trauma, Surg., Gynec. & Obst. **61**:369-378 (Sept.) 1935.

favoring the development of thrombosis in veins there. Slowing of the circulation alone probably does not cause thombosis, but experience shows that thrombosis develops in regions where the circulation is slow, that is, in the veins of the lower extremities and in the auricular appendages of the heart. The circulation in the veins is maintained by the drive of the arterial circulation, contraction of the skeletal muscles, negative intrathoracic pressure in inspiration and the plunger-like action of the liver in squeezing blood out of the abdomen. Operations on the abdomen tend to disturb this venous circulation. The blood pressure is apt to fall, especially if there is cardiac disease. The patient lies quietly on his back for many days, and the legs are not moved, so that muscular contractions no longer help the venous blood to return to the abdomen. Because of pain, bandages and adhesive tape the abdomen is quiet and the respiratory excursions are shallow. As a result, the suction action of the changes in the intrathoracic pressure and the plunger action of the liver are reduced to a minimum. It has been shown by Blumgart and Weiss [11] that in the presence of cardiac insufficiency the circulation time is prolonged, the velocity of venous return flow is reduced and the veins of the lower extremity suffer first.

In addition to slowing of the circulation, other factors probably instrumental in producing postoperative thrombosis are increase in the number of blood platelets, liberation of increased amounts of tissue juices into the circulation and a return to a full diet with increased protein intake.

11. Blumgart, H. L., and Weiss, S.: Clinical Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, J. Clin. Investigation 4:15-31 (April) 1927; III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Rheumatic and Syphilitic Heart Disease, ibid. 4:149-171 (June) 1927; IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Arteriosclerosis and in Patients with Arterial Hypertension, ibid. 4:173-197 (June) 1927; V. The Physiological and the Pathological Significance of the Velocity of Blood Flow, ibid. 4:199-209 (June) 1927; VI. The Method of Collecting Active Deposit of Radium and Its Preparation for Intravenous Injection, ibid. 4:389-398 (Aug.) 1927; VII. Pulmonary Circulation Time in Normal Resting Individuals, ibid. 4:399-425 (Aug.) 1927; VIII. Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, ibid. 4:555-574 (Oct.) 1927; IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to the Heart, and Related Aspects of the Circulation in Patients with Cardiovascular Disease, ibid. 5:343-377 (Feb.) 1928; X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients with Cardiovascular Disease Compared with Similar Measurements in Fifty Normal Persons, ibid. 5:379-392 (Feb.) 1928.

Thrombosis begins with a deposit of blood platelets on the vessel linings. Brock[12] discussed the increased platelet count observed after operations and post partum and noted that the peak of this count was reached at about ten days, corresponding with the usually observed occurrence of thrombosis.

Galloway[13] noted that the platelets increased up to 180 per cent in 10 cases in which embolism followed fracture.

Perhaps the only common factor in the occurrence of all thromboses is the liberation of increased amounts of tissue juices into the circulation. Pickering and Mathur[14] found that the ingress of tissue juices into the circulation induces hypercoagulability and later an increase of platelets but does not suffice for the inception of thrombosis. Both factors are important in the inception or growth of thrombi when the condition of the blood plasma favors the deposition and clumping of the platelets or when the stability of plasma colloids is reduced.

The influence of diet on the agglutinability of platelets has been noted by Pickering and Mathur. This agglutinability is much less after a meal of carbohydrates than after one of meat. Mills[15] reported that in postoperative, postfebrile and postpartum conditions the platelet count, which has been sharply decreased in pregnancy or fever, begins to rise. It reaches a peak on the eighth to the eleventh day after the fever subsides or after delivery. It then returns to normal in four or five days. This rise in the platelet count usually occurs when the patient is allowed to be up for mild exercise and when full diet is resumed. The increased protein intake increases the tendency of the platelets to clump and disintegrate.

Obesity.—Pulmonary embolism following operation more often causes death in the obese than in persons of average weight. Snell[16] studied the relation of obesity to postoperative embolism at the Mayo Clinic and concluded that "there is a group of patients over 50 years of age, obese and with normal or subnormal blood pressure, who are particularly susceptible." Eight of the 13 postoperative deaths in our series occured in overweight patients.

12. Brock, R. C.: Postoperative Venous Thrombosis and the Platelet Count, Lancet **1**:688-690 (April 1) 1933.

13. Galloway, J. F.: The Blood Platelets After Fracture, Lancet **1**:1082 (May 16) 1931.

14. Pickering, J. W., and Mathur, S. N.: Role of Tissue Juices in Thrombosis, Lancet **2**:387-388 (Aug. 20) 1932.

15. Mills, C. A.: Relation of Protein Diet to Thrombosis, Ann. Surg. **91**:489-491 (April) 1930.

16. Snell, A. M.: The Relation of Obesity to Fatal Postoperative Pulmonary Embolism, Arch. Surg. **15**:237-244 (Aug.) 1927.

In summing up the available data on our first point, the necessity of appreciating the increased risk of pulmonary embolism in certain persons and in certain type of operations, we would stress the following factors:

The patient under 30 runs little risk. The greatest risk is between the ages of 40 and 60.

A woman of susceptible age runs a slightly greater risk of postoperative embolism than does a man. After an accidental injury the risk is three times as great for the female, probably because of the greater incidence of varicose veins.

Operations on the abdomen and the pelvis subject the patient to much greater risk of complicating embolism than do extra-abdominal operations. Exploratory laparotomy for inoperable malignant tumor, colostomy, enterostomy, herniotomy and resection of the intestine carry the greatest danger of this complication.

Disease of the heart increases the threat of embolism because of a failure to maintain efficient circulation.

A patient who is overweight, especially if over the age of 50 and with a normal or subnormal blood pressure, faces a greater risk of embolism.

ADVANTAGE OF RECOGNIZING NONFATAL EMBOLISIM AND PREMONITORY SIGNS OF FATAL EMBOLISM

Recognition of nonfatal embolism suggests extreme caution in subsequent treatment. A more prolonged stay in bed is indicated. The patient should not be allowed even to go to the bathroom. Bowel movements should be facilitated by liquid petrolatum or by enemas.

Postmortem evidence of previous nonfatal embolism was observed in 8 of our cases. The lower lobes of both lungs were the sites of the resulting infarcts in 4 instances, while in each of 3 patients one lower lobe only was involved. The average time of appearance of the embolism for the entire group was five days after the onset of illness.

One will more accurately recognize embolism if shock is the criterion for diagnosis. Cyanosis and dyspnea are not cardinal symptoms. In cases of nonfatal embolism one should look for minor grades of the same symptoms most frequently observed in our fatal cases—perspiration, imperceptible pulse, weakness and pain in the chest. Barnes pointed out that the common picture is "shock, with or without dyspnea, with faintness, pallor, sweating, acceleration of the pulse, a marked fall in blood pressure, vomiting and sometimes collapse." In many instances an infarct will be produced, and the classic signs of rise in temperature, cough, pleural friction rub, roentgenographic signs of pulmonary consolidation and hemoptysis will follow. In some cases, however, no

infarct is produced, as the collateral circulation in the lung is sufficient to care for the embolism. In such a case the shock syndrome in varying degrees makes the diagnosis.

The embolus may be massive but nonlethal. White[17] stated that in this condition the right ventricle and the pulmonary conus dilate, producing pulsation in the second and third left interspaces, with a loud systolic murmur there and an accentuated P wave in lead II. Friction rub and gallop rhythm may be present. The cervical veins may be dilated and pulsing, and extreme cyanosis develops. The roentgenogram may reveal accentuation of the hilus shadow on the occluded side, and Camp[18] stated the opinion that this is due to dilatation of the pulmonary vessels. White,[17] McGinn and White[19] and Barnes[20] reported electrocardiographic changes characteristic of acute pulmonary embolism by which it can be differentiated from coronary thrombosis. Barnes

TABLE 1.—*Symptoms of Fatal Pulmonary Embolism (Twenty-Four Cases)*

15 patients	....	Sudden death
1 patient	Lived a few moments	Pain in the chest
1 patient	Lived 8 minutes	Tightness in the chest; clammy skin
1 patient	Lived 30 minutes	Cyanosis; imperceptible pulse
1 patient	Lived 35 minutes	Tightness in the chest; weakness
1 patient	Lived 1 hour	Dyspnea; weakness; restlessness
1 patient	Lived 1½ hours	Pain in the chest; slow respirations; cyanosis; imperceptible pulse
1 patient	Lived 2½ hours	Dyspnea; weakness; dizziness; headache
1 patient	Lived 3 hours	Dyspnea; weakness; slight fever; weak pulse
1 patient	Lived 24 hours	Pain in the chest; perspiration

gave reports of 2 cases in which there were mild premonitory and severe sublethal attacks and in which the electrocardiogram was diagnostic.

In our series the average time at which fatal embolism occurred in the postoperative group was sixteen days, while in the post-traumatic group it was forty-one days.

Even though the embolus is massive and lethal, death does not always occur at once, as our cases indicate (table 1).

The most common symptoms and signs are perspiration, imperceptible pulse, weakness and pain in the chest.

The next most common symptoms and signs are a tight feeling in the chest, dyspnea and cyanosis.

17. White, P. D.: The Acute Cor Pulmonale, Ann. Int. Med. **9**:115-122 (Aug.) 1935.

18. Camp, J. D., cited by Barnes.[4]

19. McGinn, S., and White, P. D.: Acute Cor Pulmonale, Resulting from Pulmonary Embolism: Its Clinical Recognition, J. A. M. A. **104**:1473-1480 (April 27) 1935.

20. Barnes, A. R.: Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, Proc. Staff Meet., Mayo Clin. **11**:11-13 (Jan. 2) 1936.

In this small group, prompt diagnosis and preparation might have allowed emergency embolectomy in 6 cases.

Lord[21] found records of 59 fatal pulmonary embolisms in the Massachusetts General Hospital. In this group only 20 per cent of the patients died in ten to twenty minutes. He stated that complete occlusion of both primary pulmonary branches kills in one to two minutes. If the patient lives longer it is presumptive evidence that occlusion is incomplete. A patient may survive total obstruction of one main branch if the sudden strain on the circulation is not too great.

Fifteen of our 24 patients died suddenly. In this group occlusion of the main pulmonary artery and its large branches was observed in 4 instances, occlusion of the right and left branches together in 5, occlusion of the common artery and one large branch in 1 and occlusion of the common artery alone in 1 and of one large branch alone in 4.

TABLE 2.—*Sites of Occlusion and Periods of Survival*

Period of Survival	Arteries Occluded		
	Common	Right	Left
Few moments	+	+	+
8 minutes	0	+	+
30 minutes	0	+	+
35 minutes	0	0	+
60 minutes	0	+	0
90 minutes	0	+	+
2½ hours	+	+	+
3 hours	+	0	+
24 hours	0	+	+

The survival periods and sites of occlusion in our other 8 cases are given in table 2.

In the patient who survived twenty-four hours both right and left branches were involved. One patient with partial occlusion of the common artery and both large branches lived two and one-half hours.

One must not think of the mechanical plug in the pulmonary arteries as large enough to block the circulation. In fact, numerous scattered small emboli in the lungs can produce the same symptom complex, and the surgeon must not be chagrined if he attempts embolectomy and finds no large plugs. In the cases we have observed it has never seemed that the emboli were large enough to block the vessels and obliterate the lumen mechanically. There is evidently an additional element of profound reflex sympathetic inhibition causing a spasm of all the pulmonary circulation. Barnes[2] cited evidence in favor of the hypothesis that sympathetic inhibition plus humoral factors of alkalinity and acidity explain the attack of shock and the sudden death.

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21. Acute Diverticulosis and Massive Pulmonary Embolism, Cabot Case 1903?, New England J. Med. **208**:260-263 (Feb. 2) 1933.

Summarizing available data on our second point, the necessity of recognizing nonfatal as well as the premonitory signs of fatal pulmonary embolism, we may conclude:

1. In many instances (33 per cent in our series) nonfatal attacks of pulmonary embolism precede the fatal attack by hours to many days.

2. Signs of nonfatal embolism or the early signs of fatal embolism are not cyanosis and dyspnea, but are those of shock, with or without dyspnea.

3. Nonfatal emboli may be small, producing only pleuritic pain, fever and rapid pulse. They may be larger and may or may not produce infarction when they lodge in the lung substance, depending on the efficiency of the circulation in the lung. They may be massive but non-lethal, with the production of acute cor pulmonale and electrocardiographic signs differing from those of cardiac infarction.

4. Fatal pulmonary embolism in 30 to 60 per cent of cases causes death within a period of thirty minutes to twenty-four hours, allowing sufficient time for operative intervention in some cases if the diagnosis can be made and the emergency is anticipated.

POSSIBILITY OF PREVENTION AND TREATMENT

First in prevention must come the realization of the problem. One must recognize the greater risk for the obese female patient over 50, with a low or normal blood pressure. Aside from the added risk of sex and age, operations on the abdomen add to the risk. Trauma with much tissue mutilation may be complicated by thrombosis and embolism. Childbirth, acute febrile disturbances (such as pneumonia or typhoid fever) and cardiac decompensations of all kinds, but especially those with auricular fibrillations, as well as all types of phlebitis, may be complicated by embolism.

Next, efforts should be made to prevent thrombosis and embolism. These are in use in some clinics. Robertson[6] on the basis of a large postmortem experience advocated in postoperative cases massage, passive and active motions of the legs, frequent moving and turning of the body and deep breathing to facilitate the circulation of blood in the dependent portions, local use of heat or of vascular stimulants, such as thyroid, used conservatively.

Walters[22] in 1930 reported the results of four and a half years' experience in attempting to reduce the incidence of postoperative embolism by giving thyroid to 4,500 patients. The incidence was only

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22. Walters, W.: A Method of Reducing the Incidence of Fatal Postoperative Pulmonary Embolism: Results of Its Use in Four Thousand and Five Hundred Surgical Cases, Surg., Gynec. & Obst. **50**:154-157 (Jan.) 1930.

0.09 per cent, as compared with 0.34 per cent in series in which thyroid was not given.

Barnes [2] stated that Willius has employed since 1926 at the Mayo Clinic centripetal massage of the legs of patients hospitalized for cardiac disease, and no deaths from massive embolism have occurred in the cardiac disease service during this period. In Gray's surgical service in the same institution a postoperative program places the patient in the Trendelenburg position for twenty-four hours after operation; carbon dioxide by inhalation is given several times day and night for the first forty-eight hours; frequent deep breathing is urged; early coughing is encouraged; the legs are kept warm on the operating table and afterward, and frequent massage of the legs practiced during the first forty-eight hours and twice daily until the patient is out of bed. With this program there have been no deaths from embolism in 750 consecutive operations, mostly laparotomies.

In view of the demonstrated effect of proteins on the tendency of platelets to agglutinate, it would seem advisable to keep the protein intake low for two weeks after operation.

Since tissue juices increase coagulability of the blood and later provoke increased platelet counts, every effort should be made to keep damage to tissues at a minimum.

Dehydration with increased viscosity of the blood favors clotting, and closer attention to fluid intake and output can be expected to cut the incidence of thrombosis.

For a patient who has had a mild nonfatal attack special care must be used to avoid a subsequent fatal attack. Greater care must be used in curtailing his efforts. He must not be allowed out of bed as soon as usual, and preparations should be made for subsequent attacks. A syringe containing ½ grain (0.032 Gm.) of papaverine hydrochloride for intravenous use should be kept at hand, as this drug tends to relieve the spasm of the pulmonary vessels. A sterile surgical set should be kept at hand if a Trendelenburg operation is to be attempted. An oxygen tent should be available.

SUMMARY AND CONCLUSIONS

Twenty-four instances of fatal pulmonary embolism in 1,781 autopsies are recorded.

The following factors favor embolism: age between 40 and 60, female sex, operations on the abdomen and the pelvis, cardiac disease and obesity with normal or subnormal blood pressure.

In our 24 cases 8 patients had nonfatal embolism preceding the fatal attack by three hours to thirty days. Such nonfatal embolism occurred on an average of five days after operation or trauma.

Shock should be the criterion for diagnosing embolism. The most common symptoms in our series were perspiration. imperceptible pulse, weakness and pain in the chest.

In our series the average postoperative fatal embolism occurred on the sixteenth day, while the death from post-traumatic embolism occurred on the forty-first day.

Fifteen patients in our series died suddenly. In this group autopsy disclosed occlusion of the main pulmonary artery and its main branches in 4 instances and occlusion of both large branches in 5.

The remaining 9 patients lived from eight minutes to twenty-four hours. allowing sufficient time for emergency embolectomy in 5 cases if conditions had been favorable.

ECTOPIC PREGNANCY, A DIAGNOSTIC PROBLEM IN GYNECOLOGY

REPORT OF A CASE

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The case here described is of interest and importance because it represents a limited group of tubal gestations in which tests for pregnancy yield negative reactions. It brings to attention, also, a limitation of the pregnancy test infrequently set forth in the literature.

An intricate diagnostic problem arose in connection with a patient with a suspected tubal abortion. The classic clinical evidence was not present. Two tests for pregnancy gave negative results, and since curettings revealed no decidual reaction, laparotomy was delayed for thirty-five days. The reason for the inadequacy of the test in this instance is clearly illustrated by the pathologic findings. Consideration of this factor is therefore of utmost value in the diagnosis of tubal abortion.

REPORT OF CASE

S. B., aged 28, had been married six years and had always had normal and regular menstrual periods. The past history was irrelevant except for an induced abortion in 1931. For four years she had been unable to become pregnant. Normal in every respect, the last menstrual period (on Dec. 8, 1937) was followed by continuous but moderate staining, and two weeks later (on December 21), when the patient was first examined, bleeding was still present.

Somatically, physical findings were within normal limits. With the exception of a walnut-sized, nontender mass in the left adnexal region, not unlike a cystic ovary, and a uterus of normal size, drawn slightly to the left, the pelvic examination revealed nothing significant.

The patient was referred to the Mount Sinai Hospital for observation, with a tentative diagnosis of ectopic pregnancy. In spite of a negative result of the Friedman test (with 2 rabbits) diagnostic curettage was performed, but in view of the absence of decidual reaction in the endometrium (fig. 1), presumptive evidence of pregnancy, and the cessation of staining, the patient was discharged from the hospital.

Ten days later, on Jan. 5, 1938, there was a normal menstrual period, which again ushered in constant uterine staining. Endocrine or blood dyscrasia, endometriosis and follicle cyst of the ovary, as well as inflammation, were then considered as causes; but the basal metabolism, the blood count, the sedimentation rate, the clotting and coagulation time, the results of urinalysis and the temperature were all within normal range. After eighteen days of staining the patient

noticed a sharp, constant ache in the left lower quadrant of the abdomen, radiating to the left lumbar region. She also voided urine frequently. The bleeding continued unchanged. At this time the mass was slightly larger but still was not tender. In view of its increasing size, laparotomy was considered imperative.
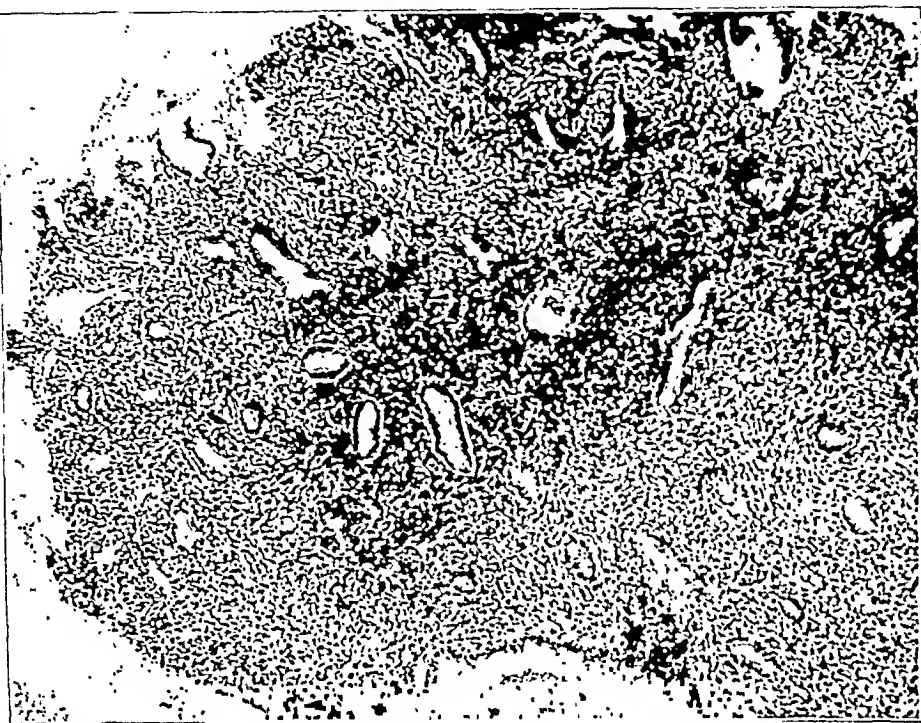
Fig. 1.—Endometrium in the resting stage found on curettage one week before the menses. No decidual reaction was noted. Secretory endometrium was also absent.
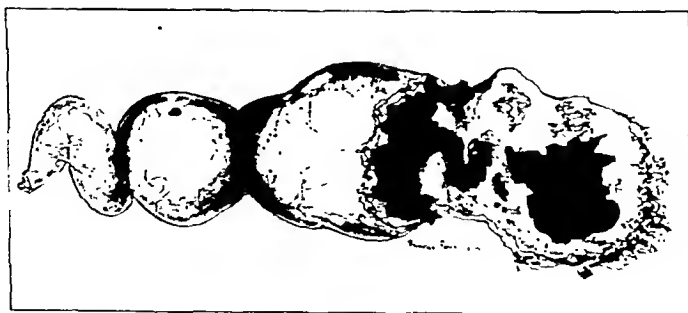
Fig. 2.—Left tube, showing the ruptured, fimbriated end and a blood clot containing villi. Note the kinking at the proximal end caused by adhesions.

The patient was again hospitalized, and at operation, on January 28, an ectopic mole was removed. The result of the Friedman test with urine catheterized preoperatively was again negative.
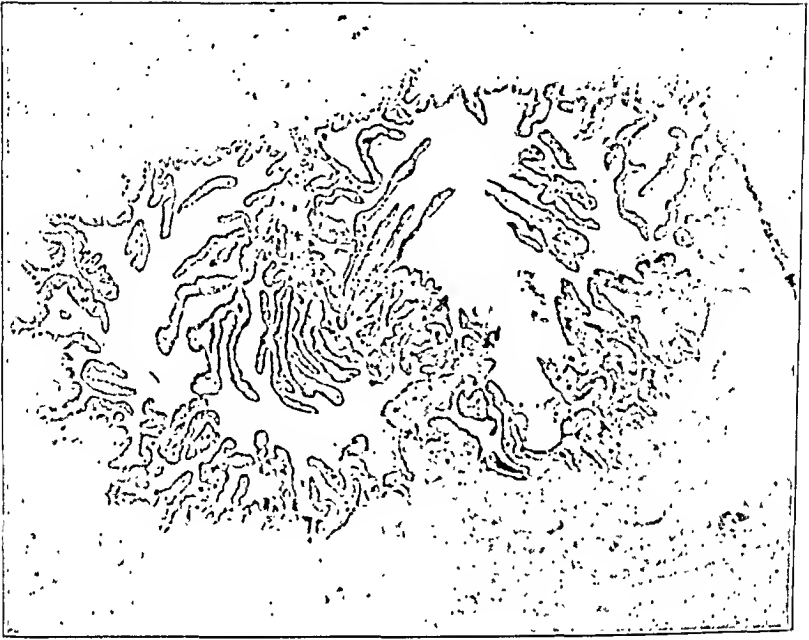
Fig. 3.—Low power photomicrograph of the cross section of the proximal end of the fallopian tube, showing chronic inflammation.

Fig. 4.—High power photomicrograph of a section of the blood clot, showing several chorionic villi.

Examination of the operative specimen revealed an enlarged left tube kinked by adhesions at the proximal end (fig. 2). Beyond the distended, gaping fimbriated portion on a bed of adhesions connecting it to the sigmoid flexure of the colon, lay a free and detached blood clot 1½ inches (3.7 cm.) in diameter; this contained the pregnancy mole, which had been completely blown out through the ruptured ampulla. There was 60 cc. of free blood in the pelvis. The left ovary, enlarged to the size of a large plum by two follicle cysts, was prolapsed.

Microscopic examination of the serial sections of the fallopian tube showed no chorionic remnants or decidual reaction (fig. 3). There was evidence of low grade inflammation. The only villi (fig. 4) observed were in the blood clot previously described. It was therefore concluded that the gestation had separated entirely from its mural attachment.

A positive result of the Friedman test is usually authentic if two test animals are used. On the other hand, the frequent false negative reactions obtained in the presence of a proved viable embryo are ascribed either to an insufficient quantity of the gonadotropic principle in the specimen of urine or to the test animals' insensitivity to that principle.

However, complete cessation of the gonadotropic response is effected also by detachment of the gestational mole from its tubal site of nidation. The pregnancy stimulus is in this manner separated from the maternal circulation. Thus the cause of the misleading negative results of the Friedman tests is made clear.

The presence of a decidual reaction in the endometrium is suggestive and significant but not pathognomonic of ectopic gestation. It is not, furthermore, a constant finding. The absence of this reaction, therefore, did not exclude the possibility of tubal pregnancy.

SUMMARY

A case of ectopic pregnancy is described.

The report is warranted because of the marked clinical atypism and because it represents a small but important group of tubal pregnancies in which the Friedman test gives negative results. The diagnostic error is therefore high. About 20 per cent of women with ectopic pregnancy are reported as giving negative reactions to this test.

The principal unusual features are: (*a*) two normal menses during a two month period of staining, (*b*) negative reactions to two Friedman tests performed within a fortnight's interval, and (*c*) curettings obtained one week before the menses, during the episode of staining, containing resting or proliferative endometrium. Decidual reaction was not observed.

A growing, nontender mass, continuous staining and a short episode of pain finally warranted laparotomy in spite of the clinical and laboratory atypism. These were the only positive findings.

The inadequacy of the Friedman phenomenon in this type of tubal abortion is due to the complete detachment of the gestation mole from the tubal wall, effecting a cessation in production of the gonado-tropic hormone and its consequent absence in the patient's urine. The tests therefore gave negative results.

This limitation of the phenomenon must always be borne in mind when a diagnosis of ectopic pregnancy is considered.

The proliferative or resting endometrium (normally present in the preovulatory phase of the menstrual interval) found in this patient one week before the menses is difficult to explain.

INTESTINAL OBSTRUCTION IN MAN

ALTERATIONS IN THE SERUM BASES AND THEIR SIGNIFICANCE

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For more than twenty-five years the alterations which take place in the chemistry of the blood during intestinal obstruction have interested many workers, who have sought to explain the course and termination of unrelieved obstruction on the basis of the changes observed in the chemical constituents of the blood. In their turn, dehydration,[1] azotemia[2] and hypochloremia following excessive loss of chloride by vomiting[3] have all been incriminated, but not one of these factors suffices to explain completely the clinical progress of patients who have intestinal obstruction. Falconer and Lyall[4] observed the changes in the constituents of the blood in a number of cases of intestinal obstruction and found that uniformity does not characterize the biochemical changes in the blood of patients who have obstruction at any particular level of the intestine. In their cases, increase in the concentration of urea in the blood was the most constant change encountered, but observations on the individual bases of the serum were not made.

1. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82-87 (July 13) 1912.

2. Cooke, J. V.; Rodenbaugh, F. H., and Whipple, G. H.: Intestinal Obstruction: VI. A Study of the Non-Coagulable Nitrogen of the Blood, J. Exper. Med. **23**:717-738 (June) 1916.

3. Haden, R. L., and Orr, T. G.: The Effect of Sodium Chloride on the Chemical Changes in the Blood of the Dog After Pyloric and Intestinal Obstruction, J. Exper. Med. **38**:55-71 (July) 1923. White, J. C., and Fender, F. A.: The Cause of Death in Uncomplicated High Intestinal Obstruction: Experimental Evidence to Show That Death Is Due Not to Toxemia, But to Loss of Digestive Fluids and Salts, Arch. Surg. **20**:897-905 (June) 1930.

4. Falconer, M. A., and Lyall, A.: Blood Chemistry in Intestinal Obstruction: Changes in Response to Treatment, Lancet **2**:1472-1477 (Dec. 25) 1937.

In 1937, Scudder, Zwemer and Truszkowski[5] reported that experimental obstruction of the alimentary tract at any level in cats was followed by elevation of the concentration of potassium in the blood to such heights as to suggest that hyperpotassemia was the cause of death. Their observations were based on determinations made on whole blood. This procedure is permissible with the cat, because in this animal the potassium content of the cells and of the plasma is similar, and the concentration in each rises and falls together. These workers ascribed the rise in the potassium concentration in the blood to the liberation of potassium from the tissues as the result of dehydration and the action of bacterial toxin, and they remarked on the similarity between the alterations they observed and those associated with Addison's disease. In a later paper[6] they showed that a similar rise in the concentration of potassium in the blood occurred in cats that had complete intestinal fistulas; in addition, Cutler and Pijoan[7] found that hyperpotassemia occurred also in dogs the intestines of which had been experimentally obstructed and that the intravenous injection of solutions of potassium chloride precipitated death.

Apart from isolated observations,[8] little notice had been taken of the changes which occur in the calcium content of the blood until Ruggieri[9] in 1935 reported that the level tended to rise after experimental obstruction and that this rise was greater the higher the level at which obstruction was present in the bowel. An explanation of the mechanism concerned was not forthcoming. As regards the other bases of the blood, particular attention has been paid in the past to alterations in the sodium content, and it has been clearly shown[10] that the concen-

5. Scudder, J.; Zwemer, R. L., and Truszkowski, R.: Potassium in Acute Intestinal Obstruction, Surgery **1**:74-91 (Jan.) 1937.

6. Scudder, J., and Zwemer, R. L.: The Effect of Complete Intestinal Fistula on Blood Potassium, Surgery **2**:519-531 (Oct.) 1937.

7. Cutler, E. C., and Pijoan, M.: Certain Chemical Factors in Experimental High Intestinal Obstruction, Surg., Gynec. & Obst. **64**:892-894 (May) 1937.

8. Hastings, A. B.; Murray, C. D., and Murray, H. A., Jr.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J. Biol. Chem. **46**:223-232 (March) 1921.

9. Ruggieri, E.: Calcemia ed occlusione intestinale, Policlinico (sez. chir.) **42**:669-684 (Nov.) 1935.

10. (*a*) Ruggieri.[9] (*b*) Gamble, J. L., and Ross, S. G.: The Factors in the Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1**:403-423 (June) 1925. (*c*) Gamble, J. L., and McIver, M. A.: A Study of the Effects of Pyloric Obstruction in Rabbits, ibid. **1**:531-545 (Aug.) 1925. (*d*) Atchley, D. W., and Benedict, E. M.: The Distribution of Electrolytes in Intestinal Obstruction, J. Biol. Chem. **75**:697-702 (Dec.) 1927. (*e*) Haden, R. L., and Orr, T. G.: The Sodium Content of the Blood of the Dog After Experimental Intestinal Obstruction, J. Exper. Med. **41**:119-127 (Jan.) 1925.

tration of this base in the plasma tends to decrease, but not to the same extent as that of plasma chloride. The total content of base in the plasma also tends to fall.[11]

These reports, particularly those dealing with the serum potassium, prompted us to ascertain whether similar variations in the serum bases occurred in clinical obstruction in man. During a period of six months, therefore, we investigated the alterations in the chemical constituents of the blood of patients who had intestinal obstruction. Our method was to collect samples of blood both during obstruction and at frequent intervals subsequently, and thereby we were able to observe not only the biochemical changes present during obstruction but the alterations which took place as the patient proceeded toward recovery or death. The findings in individual cases appear in table 1.

To obtain our quantitative data, we employed the following technical procedures: for the determination of the urea content of whole blood, the Van Slyke and Cullen modification of the Marshall aeration and titration method;[12] for chloride in plasma, the Osterberg and Schmidt method;[13] for the carbon dioxide–combining power of the plasma, the method of Van Slyke and Stadie;[14] for the sodium content of the serum, the method of Kramer and Gittleman;[15] for the potassium content of the serum, the method of Kramer and Tisdall;[16] for the calcium content of the serum, the method of Clark and Collip;[17] and for the total base content of the serum, the method of Stadie and Ross.[18]

COMMENT

These reports of cases show that during acute intestinal obstruction, both mechanical and paralytic, in man, the concentration of serum

11. Gamble and Ross.[10b]   Gamble and McIver.[10c]   Atchley and Benedict.[10d]

12. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease, and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211-228, 1914.

13. Osterberg, A. E., and Schmidt, E. V.: The Estimation of Plasma Chlorides, J. Lab. & Clin. Med. **13**:172-175 (Nov.) 1927.

14. Van Slyke, D. D., and Stadie, W. C.: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1-42 (Nov.) 1921.

15. Kramer, B., and Gittleman, I.: An Iodometric Method for the Determination of Sodium in Small Amounts of Serum, J. Biol. Chem. **62**:353-360 (Dec.) 1924.

16. Kramer, B., and Tisdall, F. F.: A Clinical Method for the Quantitative Determination of Potassium in Small Amounts of Serum, J. Biol. Chem. **46**:339-349 (April) 1921.

17. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464 (March) 1925.

18. Stadie, W. C., and Ross, E. C.: A Micro Method for the Determination of Base in Blood and Serum and Other Biological Materials, J. Biol. Chem. **65**:735-754 (Oct.) 1925.

TABLE 1.—Summary of Cases

Case	Clinical Data	Date	Blood Urea, Mg. per 100 Cc.	Plasma NaCl, Mg. per 100 Cc.	Plasma CO₂ Combining Power, Vol. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum Ca, Mg. per 100 Cc.	Hematocrit, per Cent	Comment
1	Man aged 35; pyloric obstruction complicated by uremic intoxication; improved under medical management before operation was performed	12/29/37	58	437	105.2	....	...	....	..	On admission; retention regimen with intravenous fluids
		12/30/37	48	468	98.2	11.5	319	....	38	2,000 cc. 0.9% NaCl daily
		1/3/38	16	611	82.4	14.1	319	....	..	1,000 cc. 5% dextrose daily
		1/6/38	16	582	79.6	16.3	336	....	40	
		1/8/38	Operation performed							
		1/17/38	14	598	61.3	16.0	336	....	39	Posterior gastroenterostomy / Before discharge
2	Man aged 39; pyloric obstruction complicated by uremic intoxication; improved under medical management before operation was performed	12/3/37	60	472	93.1	12.5	...	....	46	On admission; retention regimen with intravenous fluids
		12/4/37	58	455	93.9	....	...	....	44	2,000 cc. 0.9% NaCl daily
		12/6/37	38	574	69.2	14.8	...	....		
		12/7/37	24	623	72.1	15.1	308	....	36	1,000 cc. 5% dextrose solution
		12/8/37	28	594	60.7	16.2	...	....	35	Before operation
		12/8/37	Operation performed							Posterior gastroenterostomy
		12/16/37	24	624	64.5	21.7	..	....	37	On recovery
3	Man aged 38; uremic intoxication complicating pyloric stenosis, with vomiting secondary to a penetrating duodenal ulcer; responded to medical management prior to operation	3/2/38	66	578	74.9	17.6	319	....	40	On admission; retention regimen and intravenous saline and dextrose solutions daily
		3/4/38	34	561	64.5	16.8	319	12.2	42	Improvement
		3/9/38	30	511	76.6					Partial gastrectomy
		3/9/38	Operation performed							
		3/21/38	27	578	57.3	16.0	308	9.6	33	On recovery
4	Man aged 59; uremic intoxication and debility complicating carcinomatous obstruction of pyloric antrum; improved with retention regimen and intravenous saline solution; operation followed by recovery	3/5/38	46	578	60.7	23.0	313	....	36	On admission; retention regimen and intravenous saline solutions
		3/7/38	33	676	66.4					Improvement
		3/9/38	22	627	58.9	19.4	319	9.5	35	Partial gastrectomy
		3/9/38	Operation performed							
		3/21/38	30	594	66.4	17.5	313	7.9	30	On recovery
		4/1/38	16	578	65.5	18.6	302	8.8	40	11 days later
5	Man aged 33; mild degree of alkalosis complicating pyloric stenosis with vomiting; relief followed medical management prior to operation	2/8/38	42	561	73.0	18.0	331	9.2	34	Retention regimen with 2,000 cc. Ringer's solution intravenously daily
		2/10/38	30	560	72.1					
		2/11/38	26	594	69.2	16.8	317	9.0	32	Posterior gastroenterostomy
		2/11/38	Operation performed							
		2/22/38	32	602	57.9	18.6	308	8.4	31	On recovery

No.	Clinical note	Date								Remarks
6	Man aged 37; mild degree of alkalosis complicating pyloric stenosis with vomiting; responded to medical management prior to operation	12/11/37	32	587	70.2	13.6	319	....	10	Retention regimen; Intravenous saline solutions daily 250 c.c. blood transfusion Posterior gastroenterostomy On recovery
		12/16/37	21	639	61.0	15.2	302	....	12	
		12/17/37	Operation performed						12	
		1/21/38	16	578	61.9	21.1	319	....	12	
7	Man aged 18; mild degree of alkalosis complicating pyloric stenosis with vomiting; responded to medical management prior to performance of operation	2/16/38	26	511	70.2	26.0	308	0.2	21	Retention regimen; intravenous saline solutions daily 500 c.c. blood transfusion Posterior gastroenterostomy Fourth day after operation On recovery
		2/19/38	18	618	55.0	29.1	292	9.2	20	
		2/21/38	18	592	34.0	21.0	298	9.6	25	
		2/21/38	Operation performed							
		2/28/38	12	571	65.1	23.0	292	9.0	21	
		3/8/38	20	581	58.9	23.8	292	19.0	25	
8	Man aged 57; acute obstruction of gastro-jejunostomy stoma which commenced 1 days prior to admission; treated conservatively (retention regimen, intravenous fluids, gastric aspirations) with definite improvement in patient's general condition but severe gastric retention (as much as 2,100 c.c. daily) persisted and was relieved only by operation	1/3/38	100	581	58.0	19.8	308	19.1	...	On admission; Intravenous Ringer's and dextrose solutions daily General condition improving but severe degree of gastric retention persisting Reduction of acute angulation of efferent jejunal loop Uneventful convalescence; discharged from hospital
		1/4/38	60	159	33.9	21.7	308	9.2	12	
		1/6/38	82	585	69.3	11.7	319	0.3	12	
		1/13/38	16	551	71.0	11.8	291	8.9	16	
		1/16/38	22	671	68.3					
		4/13/38	Operation performed							
9	Boy aged 3 years; signs of acute intestinal obstruction developed while in hospital; operation disclosed internal herniation of the jejunum through surgical hiatus; improvement followed surgical relief, but edema of the extremities developed post-operatively; this disappeared when saline therapy was discontinued	1/22/38	16	582	65.3	15.0	319	2.5	...	On admission; no obstruction Signs of obstruction developed; intravenous saline solutions commenced Immediately before operation 12 hours after operation Obstruction relieved; edema present; saline discontinued On recovery
		1/27/38	20	580	60.7	14.9	319	5.7	...	
		12/30/37	16	189	65.1	...	...	...	...	
		1/1/38	150		65.5	...	...	...	...	
		1/2/38	81	611					...	
		1/2/38	Operation performed	710		12.1	312	...	11	
		1/3/38	16	627	...	11.0	258	...	...	
		1/6/38	30	591	62.6	22.0	322	...	...	
10	Man aged 65; obstructed ventral hernia involving midileum; acute symptoms for two days; responded to conservative management (duodenal suction and intravenous fluids) prior to operation	1/19/38	22	611	42.9	17.0	319	8.9	29	On admission; Intravenous saline and dextrose solutions daily Definite improvement Operative repair of hernia On recovery
		2/11/38	12							
		2/11/38	30	611	67.0	19.3	319	9.3	31	
		2/28/38	Operation performed	591	71.0	16.3	292	8.1	32	
		2/28/38	26							
11	Woman aged 51; obstructed incisional hernia involving small bowel (roentgeno-logic diagnosis); responded to conservative treatment	3/9/38	28	627		18.5	325	8.8	11	On admission; occasional vomiting; symptoms mild On recovery
		3/11/38	29	627	60.7	17.5	308	10.2	11	
		3/22/38	24	602	58.9	17.5	308	9.9	10	

TABLE 1.—Summary of Cases—Continued

Case	Clinical Data	Chemical Examination of the Blood								Comment
		Date	Blood Urea, Mg. per 100 Cc.	Plasma NaCl, Mg. per 100 Cc.	Plasma CO₂ Combining Power, Vol. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum Ca, Mg. per 100 Cc.	Hematocrit, per Cent	
12	Woman aged 79; acute obstruction of ileum (roentgenologic diagnosis); duration one or two days; responded to conservative management with intravenous saline solutions and duodenal suction; although concentration of serum potassium was not determined during period of obstruction, note rise on recovery	3/23/38	96	503	....	....	...	...	...	During obstruction; saline solutions given prior to analysis of blood
		3/28/38	26	600	58.9	10.2	313	7.5	35	Obstruction relieved; no further saline solutions given
		4/1/38	23	561	65.5	15.8	312	8.4	39	On recovery
13	Woman aged 86; acute obstruction of terminal ileum attributable to intraperitoneal adhesions (roentgenologic diagnosis); treated conservatively with duodenal suction, intravenous fluids; death ensued	12/8/37	44	569	53.2	20.4	...	...	40	On admission; nasal suction and intravenous saline solutions
		12/9/37	78	563	37.2	15.9	...	8.3	41	Before death
14	Woman aged 47; acute obstruction of transverse colon attributable to intra-abdominal adhesions (roentgenologic diagnosis); treated conservatively by means of duodenal suction and intravenous saline solutions; recovery ensued	12/4/37	50	470	80.6	14.5	...	...	34	Before treatment was instituted;
		12/6/37	46	549	63.6	14.5	...	9.5	33	2,000 cc. 0.9% NaCl daily
		12/8/37	24	577	60.7	15.1	...	...	34	Intravenous fluids discontinued
		12/22/37	18	550	67.3	17.8	...	...	37	On recovery
15	Woman aged 64; carcinoma of rectum obstructing lumen; treated conservatively by means of intravenous saline solutions, stupes to abdomen and rectal irrigations; relief of obstructive symptoms ensued	1/3/38	48	611	50.4	17.2	325	8.7	46	On admission; conservative treatment with intravenous saline solutions, stupes and rectal irrigations
		1/3/38	42	651	56.0	19.0	...	9.3	..	
		1/6/38	26	635	60.7					Symptoms relieved
		1/7/38	16	594	63.4	19.3	342	9.8	45	
16	Woman aged 42; acute-on-chronic obstruction from carcinoma of the rectum of 4 days' duration; management conservative; complete relief followed performance of operation	12/15/37	32							On admission; prepared for operation
		12/19/37	Operation performed........	619	64.5	18.5	...	...	30	Colostomy
		1/12/38	18	578	65.5	22.9	313	...	36	On recovery
17	Woman aged 55; acute-on-chronic obstruction from carcinoma of sigmoid colon; failed to respond to conservative measures; at operation, colonic distention grade 3 was found; recovery ensued	11/23/37	24	594	65.5	14.7	...	...	41	On admission; dextrose and saline solutions intravenously
		11/21/37	34	611	59.8	14.2	...	9.3	33	Before operation
		11/21/37	Operation performed........							Laparotomy; colostomy
		12/9/37	18	563	57.0	19.5	...	...	37	On recovery

	Clinical data	Date								Remarks
18	Woman aged 43; thrombosis of the superior mesenteric vessels following operation for partial and intermittent jejunal obstruction	3/ 3/38	21	635	67.0	10.0	392	...	...	On admission; occasional vomiting only
		3/ 5/38	61	710	63.9	13.8	3:0	8.9	36	Resection of several coils of jejunum; saline solution given intravenously
		3/ 9/38	70	775	50.1	15.3	351	8.7	31	Third day after operation; saline solution given intravenously. Died 24 hours later
19	Man aged 65; postoperative distention following left inguinal colostomy; relieved by conservative measures (duodenal suction, intravenous saline solutions, hot abdominal packs); recovery occurred	11/17/37	10	680	50.1	15.9	...	...	11	Second day after operation; treatment begun
		12/14/37	32	521	61.3	18.2	...	...	12	On recovery
20	Woman aged 59; moderate degree of postoperative distention following colostomy for carcinoma recti; colostomy loop opened on second day; treated conservatively, with recovery	2/ 3/38	14	683	59.8	14.2	315	9.7	22	Third day after operation; receiving saline solutions intravenously
		2/14/38	20	563	64.1	14.6	798	9.3	34	Seven days after clinical recovery
		2/21/38	11	590	64.5	29.6	389	10.6	34	Fourteen days after clinical recovery
21	Woman aged 42; general peritonitis with paralytic ileus following right hemicolectomy for carcinoma of ascending colon; death occurred five days after operation; the single serum potassium reading was obtained during a period of extreme distention	11/24/37	61	620	65.9	29.3	...	...	10	Fourth day after operation; receiving solutions of dextrose and saline solutions intravenously
		11/25/37	91	619	65.7	...	...	...	.	died a few hours later
22	Man aged 48; generalized peritonitis with paralytic ileus following laparotomy which revealed inoperable carcinoma of colon; died three days after operation	2/18/38	72	585	44.7	21.1	362	0.8	51	Condition of the blood a few hours before death
23	Woman aged 70; paralytic ileus from peritonitis following anterior resection of sigmoid colon; treated conservatively with duodenal suction, intravenous saline solutions, hot abdominal packs; death ensued	11/30/37	42	673	59.9	...	...	...	10	Fourth day after operation
		12/ 1/37	51	653	62.6	15.0	...	11.0	11	Condition deteriorating; died 12 hours later
24	Woman aged 56; paralytic ileus following sigmoid colostomy performed 12/11/37; treated conservatively with duodenal suction, intravenous fluids and hot abdominal packs; death ensued; at necropsy, generalized peritonitis was observed	12/17/37	31	620	63.5	17.2	...	...	33	Third day after operation; gross abdominal distention
		12/18/37	42	687	67.0	21.6	...	...	30	Improved
		12/20/37	21	591	61.0	16.8	...	...	35	Relapse; severe degree of distention
		12/22/37	38	541	61.7	16.5	...	...	35	Improved
		12/24/37	28	802	73.0	...	...	...	. :	Condition deteriorating
		12/27/37	10	670	74.2	16.5	...	...	.	Died 24 hours later
		12/29/37	11	497	73.2	16.2	363	...	.	

TABLE 1.—Summary of Cases—Continued

Case	Clinical Data	Date	Blood Urea, Mg. per 100 Cc.	Plasma NaCl, Mg. per 100 Cc.	Plasma CO₂ Combining Power, Vol. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum Ca, Mg. per 100 Cc.	Hematocrit, per Cent	Comment
25	Woman aged 58; acute obstruction of colon following ingestion of barium sulfate meal in presence of carcinoma of sigmoid colon; obstruction relieved by conservative means; colostomy then performed preliminary to later radical excision of growth; patient showed a severe degree of listlessness which improved after the addition of potassium and calcium salts to the intravenous solutions	1/ 9/38	34	594	54.0	....	328	10.2	36	On admission; intravenous dextrose and saline solutions daily
		1/11/38	16	...	...	20.0	322	...	36	Obstruction relieved but listlessness present
		1/13/38	14	...	...	11.8	319	8.8	...	
		1/15/38	14	585	68.3	11.9	322	...		Third day after operation
		1/15/38	Operation performed							
		1/18/38	14	611	65.5	14.3	316	8.6	35	Intravenous dextrose solutions daily
		1/18/38	Received 2 Gm. KCl and 1 Gm. CaCl₂							
		1/19/38	14	563	73.0	14.5	325	8.8	36	General condition improving
		1/19/38	Received 4 Gm. KCl and 2 Gm. CaCl₂							
		1/21/38	24	569	71.1	14.9	325	9.2	41	Definite improvement; intravenous fluids stopped
		1/24/38	26	575	66.4	17.3	324	9.8	40	On recovery
		1/24/38	Received 4 Gm. KCl and 2 Gm. CaCl₂							
		1/26/38	22	569	65.5	22.0	313	9.7	41	
		1/31/38	32	619	58.9	20.3	308	9.8	38	
29	Woman aged 69; paralytic ileus following exteriorization of sigmoid colon for diverticulitis; treated conservatively (duodenal suction, intravenous fluids) with restoration of function of bowel on the 11th day; definite languor persisted until potassium and calcium salts were added to the intravenous fluids following the fifteenth day	12/17/37	44	710	60.7	16.0	...	...	36	Fourth day after operation; intravenous dextrose and saline solutions daily
		12/18/37	48	627	57.0	11.1	...	...	36	
		12/19/37	51	669	54.1	10.7	...	...	38	Bowels functioning well but severe languor present
		12/21/37	40	683	51.3	9.5	...	...	40	Intravenous dextrose solutions daily
		12/24/37	24	647	63.3	12.8	336	...	39	
		12/26/37	18	567	73.0	11.6	342	7.7	39	
		12/29/37	24	483	89.6	8.7	325	8.7	39	
		12/29/37	Received 1 Gm. KCl and 1 Gm. CaCl₂			9.9	328	9.0	42	Intravenous NaCl solutions restored
		12/30/37	24	479	83.4					
		12/30/37	Received 2 Gm. KCl and 1 Gm. CaCl₂	541	82.4	10.1	328	8.8	39	
		12/31/37	24							
		12/31/37	Received 2 Gm. KCl and 1 Gm. CaCl₂	583	53.0	12.1	342	8.5	37	Definite improvement; intravenous solutions discontinued
		1/ 2/38	18	594	79.6	17.2	325	9.2	39	
		1/ 5/38	26	594	69.2	16.4	323	9.4	38	On recovery
		1/ 7/38	26	587	59.0					
		1/10/38	26							
27	Man aged 70; paralytic ileus following temporary ileostomy performed for subacute obstruction secondary to carcinoma of the cecum; treated conservatively (duodenal suction, intravenous fluids, etc.) with eventual recovery; definite improvement followed the addition of potassium and calcium salts to the intravenous solutions	1/29/38	40	627	56.0	16.3	330	7.8	...	First day after operation; intravenous dextrose
		1/31/38	16	660	58.9	13.9	313	7.5	32	Saline and dextrose solutions daily
		2/ 2/38	20	619	...	...	...	...	...	500 cc. blood transfusion
		2/ 2/38	Received 1 Gm. CaCl₂							
		2/ 4/38	24	611	57.0	11.2	313	8.0	38	Dextrose solutions only
		2/ 4/38	Received 2 Gm. KCl and 1 Gm. CaCl₂							
		2/ 5/38	26	563	63.5	12.5	308	7.7	...	
		2/ 5/38	Received 3 Gm. KCl and 3 Gm. CaCl₂							
		2/ 7/38	16	553	62.5	11.1	290	8.0	...	
		2/ 7/38	Received 2 Gm. KCl and 2 Gm. CaCl₂							
		2/ 9/38	18	578	65.5	12.6	313	8.2	35	Definite general improvement; duodenal suction discontinued; NaCl and dextrose solutions restored
		2/ 9/38	Received 2 Gm. KCl and 2 Gm. CaCl₂							
		2/12/38	...	591	57.0	12.6	302	8.8	40	500 cc. blood transfusion
		2/12/38	Received 3 Gm. KCl and 2 Gm. CaCl₂							
		2/13/38	14	591	54.1	18.7	296	8.8	40	
		2/13/38	Received 4 Gm. KCl and 2 Gm. CaCl₂							
		2/16/38	22	572	54.1	14.3	272	8.4	37	Left hospital

potassium, instead of rising as it does in animals, tends to fall, often to a considerable degree. The concentrations of sodium and calcium in the serum tend to fall also, but their reduction is less severe than is that of potassium.

According to most authorities,[19] the potassium content of the serum in health ranges between 18 and 22 mg. per hundred cubic centimeters, but values outside these limits occasionally are found in healthy persons. Because of this wide range, the decision of whether or not the concentration of serum potassium in individual cases is altered should rest on changes found on repeated estimations rather than on single observations. The highest value that we observed for potassium was 26 mg. per hundred cubic centimeters of serum (case 7), a level which was maintained on recovery. On the other hand, the lowest value encountered was 9.5 mg. per hundred cubic centimeters (case 26). In 16 cases values less than 16 mg. per hundred cubic centimeters of serum were encountered (cases 1, 2, 6, 8, 9, 12, 13, 14, 17, 18, 19, 20, 23, 25, 26 and 27).

Since we began this investigation, Scudder, Zwemer and Whipple [20] have published their observations on 25 clinical cases of intestinal obstruction. Taking as the normal value for potassium 18 to 21 mg. per hundred cubic centimeters of plasma, they found that of 20 cases in which the blood was examined before saline therapy was begun, the potassium content of the plasma was elevated in 7 cases and decreased in 5. The highest reading recorded was 33.4 mg., and the lowest 13.4 mg., per hundred cubic centimeters. It is interesting to note that higher values than these have been found in the presence of other conditions. Keith and Binger [21] noted that 3 normal persons had concentrations of potassium of 33, 37 and 40 mg. per hundred cubic centimeters of serum respectively after the ingestion of potassium salts, without ill effects.

Our findings in clinical cases of intestinal obstruction are at variance with the published observations in cases of experimental obstruction in cats and dogs. However, we, too, have observed increase in the concentration of serum potassium in 3 dogs (table 2) in which the upper-

19. Whelan, M.: The Effect of Intravenous Injection of Inorganic Chlorides on the Composition of Blood and Urine, J. Biol. Chem. **63**:585-620 (April) 1925. Hoffman, W. S., and Jacobs, H. R. D.: The Partition of Potassium Between the Serum and Corpuscles in Health and Disease, J. Lab. & Clin. Med. **19**:633-644 (March) 1934. Kramer and Tisdall.[16]

20. Scudder, J.; Zwemer, R. L., and Whipple, A. O.: Acute Intestinal Obstruction: Evaluation of Results in Two Thousand One Hundred and Fifty Cases, with Detailed Studies of Twenty-Five Showing Potassium as a Toxic Factor, Ann. Surg. **107**:161-197 (Feb.) 1938.

21. Keith, N. M., and Binger, M. W.: Diuretic Action of Potassium Salts, J. A. M. A. **105**:1584-1590 (Nov. 16) 1935.

most loop of the jejunum was completely obstructed. These dogs lived five, six and eight days respectively before severe intoxication occurred. During these periods, other alterations in the constituents of the blood, such as azotemia, hypochloremia, alkalosis and dehydration, were observed; in all 3 dogs the concentration of the sodium and total bases

TABLE 2.—*Changes in Constituents of the Blood Following High Jejunal Obstruction*

Dog	Day	Blood Urea, Mg. per 100 Cc.	Plasma NaCl, Mg. per 100 Cc.	Plasma CO_2-Combining Power, Vol. %	Serum Na, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Ca, Mg. per 100 Cc.	Serum Protein, Gm. per 100 Cc.	Total Base, Cc. N/10 NaOH	Hematocrit, per Cent
1	Before	30	619	50.4	354	29.0	11.3	...	170	46
	1	16	632	46.6	348	33.2	11.2	6.9	...	52
	2	28	597	50.4	342	37.6	11.2	...	...	42
	3	16	573	49.4	331	37.3	10.2	...	...	46
	4	24	...	....	308	36.7	11.4	...	...	41
	5	..	...	....	...	....	....	...	...	45
	6	24	491	56.0	296	30.2	10.4	...	...	..
	7	...	..	....	...	....	....	...	...	51
	8	24	463	71.0	308	36.9	9.4	6.9	151	
2	Before	26	679	46.6	336	20.9	9.8	6.1	160	38
	1	22	573	47.5	331	19.3	9.2	...	...	40
	2	54	556	54.1	342	24.4	11.8	...	...	44
	3	..	...	....	...	....	....	...	...	43
	4	34	456	57.9	325	25.0	11.0	...	...	40
	5	44	421	62.6	290	23.0	9.6	...	...	50
	6	88	398	49.0	308	34.1	10.6	8.5	151	
3	Before	27	644	44.7	359	24.1	13.8	8.7	172	57
	1	16	544	46.7	347	25.3	11.3	...	...	57
	2	18	528	57.0	336	27.0	8.1	...	...	..
	3	22	480	62.6	313	28.4	6.9	...	...	56
	4	68	456	....	296	42.6	11.8	...	...	63
	5	186	412	46.6	307	38.3	12.4	9.2	150	59

TABLE 3.—*Comparison of the Distribution of Sodium and Potassium in the Blood of Man, Dogs and Cats*

	Cells		Plasma	
	Sodium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Sodium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.
Man......................	22	408	313	19
Man......................	27	415	331	17
Dog......................	208	20	342	20
Dog......................	211	17	330	17
Cat......................	337	38	388	32
Cat......................	217	41	336	34

of the serum decreased greatly, whereas the concentration of calcium in the serum tended to remain within normal limits. However, in contrasting the behavior of the serum potassium during obstruction in human beings and in animals, it must be remembered that the distribution of sodium and potassium between the cells and the plasma of the blood differs vastly in the two groups. Table 3 shows that whereas in dogs and cats there is the same concentration of potassium in the cells as in the plasma, in human beings the concentration of potassium in

the cells is twenty times that in the plasma, and the relation of sodium to potassium in the blood cells in man is just the opposite of that in experimental animals. These facts make it difficult to presume that the potassium of the blood has the same function in the economy of the animal that it has in that of human beings.

FACTORS AFFECTING THE SERUM POTASSIUM DURING INTESTINAL OBSTRUCTION IN MAN

It is obvious from a perusal of our findings in clinical cases that, because alterations in the concentration of serum potassium during obstruction do not occur constantly, they are secondary to other factors. Indeed, all the changes which occur in the constituents of the blood during obstruction appear to be secondary to the onset of clinical intoxication and exert but a contributory influence on the fatal termination.[22] When one considers the mechanism by which the decrease in the concentration of potassium in the serum is brought about, three possible factors present themselves. These will now be dealt with in turn.

TABLE 4.—*Composition of the Secretions Aspirated from the Stomach in Clinical Cases of Intestinal Obstruction*

	Case									
	1	2	3	4	5	6	7	8	9	10
Volume for 24 hours, cc	2,500	2,250	1,900	1,750	1,350	1,230	1,050	1,000	860	670
Cl content, mg. per 100 cc	514	271	191	169	377	226	194	375	371	497
Na content, mg. per 100 cc	256	135	164	115	267	164	55	112	129	213
K content, mg. per 100 cc	83	28	57	43	89	62	41	52	51	44

The first and probably the most potent factor is the great loss of potassium from the body which occurs as the result of vomiting or aspiration of retained gastric contents. This observation has been noted previously by Scudder and his associates.[23] Table 4 contains some data concerning the amounts of potassium which may be lost in the course of twenty-four hours in cases in which continuous gastric aspiration is employed. In spite of sips of water by mouth, the concentration of potassium in specimens of the gastric contents was two to four times that in the serum. The stomach is responsible for this active loss of potassium (table 5), because the gastric secretions alone have a high content of potassium, whereas the remaining gastrointestinal secretions, including the succus entericus,[24] have lower concentrations of potassium. It is

22. Falconer, M. A.: Clinical Aspects of the Blood Chemistry in Intestinal Obstruction, Proc. Staff Meet., Mayo Clin. **13**:460-464 (July 20) 1938.

23. Scudder, Zwemer and Truszkowski.[5] Scudder, Zwemer and Whipple.[20]

24. de Beer, E. J.; Johnston, C. G., and Wilson, D. W.: The Composition of Intestinal Secretions, J. Biol. Chem. **108**:113-120 (Jan.) 1935.

interesting to note that this same factor of loss of potassium in the gastric contents during obstruction has been observed in cats by Scudder [5] and his associates and in dogs by us.

The second factor for consideration is the possible antagonism of sodium and potassium in the blood, as was first suggested by Bunge in 1873.[25] The majority of our subjects were given solutions of sodium chloride intravenously, and often the concentration of potassium in the serum continued to decrease after saline therapy was instituted, especially in cases (cases 8, 13, 25, 26 and 27) in which gastric or duodenal suction was continued. Although both Scudder [20] and we observed low concentrations of serum potassium before treatment was commenced, we performed the following experiments in order to test this possibility.

The principle on which our experiments were based was to give a healthy male volunteer large amounts of sodium chloride, at the same time restricting his intake of potassium, in order to ascertain the effect

TABLE 5.—*Composition of Normal Digestive Secretions (Four Examples of Each)*

	Fasting Stomach Secretions				Fasting Duodenal Secretions				T Tube Bile			
Cl content, mg. per 100 cc..........	422	401	292	248	404	376	269	222	407	357	342	336
									309	298	306	361
Na content, mg. per 100 cc..........	9	37	181	181	292	240	191	142	10	9	9	29
K content, mg. per 100 cc..........	93	98	107	49	20	17	29	20				

on the concentration of potassium in the serum. Throughout the periods of observation our subject continued at his work, and after 1 experiment a period of a month was allowed to elapse before a second experiment was begun. We first administered a diet low in potassium, prepared according to the methods of Sister Mary Victor [26] and containing known amounts of potassium with an energy content of at least 2,200 calories per day. The results are summarized in table 6. This regimen was without significant effect on the values for serum potassium, the hematocrit indexes of the blood or the weight. In our second experiment the same diet was used and, in addition, 1,000 cc. daily of a solution of 2 per cent sodium chloride was given intravenously (table 7). The concentration of potassium decreased within three days to 15.5 mg. per hundred cubic centimeters of serum, but with continued administration of saline solution we were unable to depress it further. In addition, the

25. Bunge, G.: Ueber die Bedeutung des Kochsalzes und das Verhalten der Kalisalze im menschlichen Organismus, Ztschr. f. Biol. **9**:104-143, 1873.

26. Mary Victor, Sister: Directions for the Planning and Preparation of Diets Low in Content of Potassium, Proc. Staff Meet., Mayo Clin. **12**:424-432 (July 7) 1937.

hematocrit indexes decreased considerably, and our subject showed a tendency to gain weight, the signs of both being evidence of retention of water. The decrease noted in the concentration of potassium in the serum, therefore, cannot be ascribed entirely to the antagonism of an

TABLE 6.—*Effect on the Chemical Constituents of the Blood of a Low Potassium Diet (Normal Male Adult)*

	Examination of Blood						Urine			
Day	Plasma NaCl, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Ca. Mg. per 100 Cc.	Hematocrit, per Cent	Weight, Pounds	Vol., Cc.	NaCl, Gm.	Na, Gm.	K, Gm.
				On Normal Diet						
1	627	325	17.6	10.3	46	164½	750	8.7	3.2	3 2
2	629	342	20.0	10.6	44	164½	700	10.1	3.3	2.7
3	627	325	18.3	10.2	46	164	1,470	7.2	2.1	2.3
			On Low Potassium Diet (1.7 Gm. K)							
4	581	331	18.3	9.8	46	163	720	9.8	3.3	3.2
5	623	331	18.0	9.9	44	162½	800	11.6	3.2	2.3
6	585	308	18.0	9.9	45	162	500	8.3	2.3	1.7
7	597	325	17.3	10 1	43	162½	610	7.9	2.7	1.3
			On Low Potassium Diet (0.8 Gm. K)							
8	644	343	18.4	10.2	44	162	620	5.9	1.3	1.8
9	594	334	19.0	10.9	44	162	570	4.8	1.7	1.7

TABLE 7.—*Effect on the Chemical Constituents of the Blood of Repeated Intravenous Infusion of Sodium Chloride Solution* *

	Examination of Blood						Urine			
Day	Plasma NaCl, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Ca. Mg. per 100 Cc.	Hematocrit, per Cent	Weight, Pounds	Vol., Cc.	NaCl, Gm.	Na, Gm.	K, Gm.
				On Normal Diet						
1	623	325	20.7	9.7	48	164½	650	9.5	1.5	2.2
2	627	336	18.9	9.9	48	164½	830	6.8	1.9	2.8
3	609	354	22.4	9.8	48	164	620	7.6	1.4	2.0
4	688	350	20.0	11.3	45	164	640	8.2	1.3	1.8
		On Low Potassium Diet (1.7 Gm. K) with 1,000 Cc. 2% NaCl Intravenously									
5	660	336	18.7	10.1	44	165½	1,250	20.7	3.0	2.9
6	635	342	17.0	9.8	42	165	2,400	30.7	5.6	1.8
7	644	325	15.5	9.9	43	166	1,250	23.5	2.9	0.8
8	660	331	15.6	9.6	40	167½	1,300	29.2	3.2	1.5
		On Low Potassium Diet (0.8 Gm. K) with 1,000 Cc. 2% NaCl Intravenously									
9	619	331	16.2	9.8	..	167½	1,420	23.9	3.3	0.9
10	651	319	15.3	9.4	41	167	1,580	27.1	3.5	0.8

* Same subject as in table 6.

excess intake of sodium, because dilution of the serum as a result of retention of water probably played a part. In a third experiment, 2 per cent Ringer's solution (sodium chloride 1.85 per cent, potassium chloride 0.10 per cent and calcium chloride 0.05 per cent) was substituted for the simple solution of sodium chloride (table 8), and there was only a slight decrease in the concentration of potassium in the serum and no significant change in the hematocrit readings or in the weight.

We deduced from these observations that although the administration of large amounts of a solution of sodium chloride will cause a slight decrease in the concentration of potassium in the blood, continued or repeated administration will not depress it further. Harrop,[27] in a review of the literature on the subject, arrived at the same conclusion. We made two other deductions: first, the addition of small quantities of potassium, as in Ringer's solution, was sufficient to protect the normal level of serum potassium from the effect of administration of sodium chloride; second, administration of Ringer's solution intravenously is less likely to lead to retention of water than is administration of simple solutions of sodium chloride. The latter opinion has been

TABLE 8.—*Effect on the Chemical Constituents of the Blood of Repeated Intravenous Infusion of Ringer's Solution* *

| | Examination of the Blood | | | | | | |
Day	Plasma NaCl, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Ca, Mg. per 100 Cc.	Hematocrit, per Cent	Weight, Pounds	Urine Volume, Cc.
			On Normal Diet				
1	611	319	20.0	9.8	46	163	900
On Low Potassium Diet (1.7 Gm. K) with 1,000 Cc. 2% Ringer's Solution Intravenously							
2	627	313	19.5	9.3	44	163½	920
3	594	325	17.9	9.4	44	163½	1,150
4	627	319	15.8	9.2	43	163½	1,150
5	635	319	17.0	9.0	44	163	1,220
On Low Potassium Diet (0.8 Gm. K) with 1,000 Cc. 2% Ringer's Solution Intravenously							
6	602	319	18.3	9.4	43	163	1,100
7	643	313	16.6	9.3	44	162½	1,140

* Same subject as in table 6.

expressed also by Coller, Dick and Maddock.[28] Similar findings resulted from a series of observations we made on patients recovering from operations on the stomach, to whom large amounts of a solution of sodium chloride were given intravenously each day and to whom only small sips of water were given by mouth. Among these patients the concentration of potassium in the serum would fall during a period of three or four days, but only to the extent of a few milligrams. Control observations of patients who were taking food by mouth did not show any significant results.

27. Harrop, G. A.: The Water and Salt Hormone of the Adrenal Cortex, Bull. Johns Hopkins Hosp. **59**:25-34 (July) 1936.

28. Coller, F. A.; Dick, V. S., and Maddock, W. G.: Maintenance of Normal Water Exchange with Intravenous Fluids, J. A. M. A. **107**:1522-1527 (Nov. 7) 1936.

It would seem, then, that in cases of obstruction in which a decrease in the concentration of serum potassium occurred during administration of saline therapy, the most potent factor in the mechanism of this decrease was the continued loss of potassium by the body by way of the aspirated gastric contents.

A third factor, possibly active in a few cases, was suggested to us by the observation of Aitken and his associates,[29] who found that the administration of dextrose to a patient suffering from familial periodic paralysis would depress the concentration of potassium to 12 mg. per hundred cubic centimeters of serum or less and would initiate an attack of paralysis. Because dextrose solutions had been given simultaneously with saline solutions to many of our patients, we selected 1 patient (case 26) for whom the concentration of potassium had been 9.5 mg.

TABLE 9.—*Dextrose-Potassium Tolerance Test*

	Case 26			Control		
Time	Blood Sugar, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.	Blood Sugar, Mg. per 100 Cc.	Serum K, Mg. per 100 Cc.	Serum Na, Mg. per 100 Cc.
Before ingestion of dextrose........	101	17.7	319	83	19.0	324
250 Gm. dextrose ingested by mouth						
1 hour later.....................	361	15.0	310	146	18.2	319
3 hours later....................	326	14.5	313	90	18.0	319
5 hours later....................	230	15.9	310	59	17.8	319

per hundred cubic centimeters of serum when obstruction was present. We gave her 250 Gm. of dextrose, following the directions of Aitken and his co-workers. The result is tabulated in table 9. Under circumstances similar to these, in Aitken's case the concentration of potassium fell to less than 8 mg. per hundred cubic centimeters of serum and remained stationary at that level until potassium chloride was given by mouth. Because no such decrease occurred in our patient and because the concentration of potassium in the serum showed a spontaneous tendency toward recovery, we presumed that the administration of dextrose was not a factor in the decrease in concentration of serum potassium previously noted in her case.

We may conclude from consideration of the three factors we have reviewed that loss of potassium in the gastric secretions is the most potent factor and that it is the only one operating in all cases.

29. Aitken, R. S.; Allott, E. N.; Castleden, L. I. M., and Walker, M.: Observations on a Case of Familial Periodic Paralysis, Clin. Sc. 3:47-57 (July 6) 1937.

EFFECTS ON KIDNEY AND BLOOD PRESSURE OF ARTIFICIAL COMMUNICATION BETWEEN RENAL ARTERY AND VEIN

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Experimental studies on hypertension have demonstrated that in dogs an elevation of blood pressure can be produced and maintained by constricting the renal artery and decreasing the flow of blood through the kidney.[1] We have reported a series of experiments in which we employed Goldblatt's method of producing hypertension. In the course of this experimental work it occurred to us that the flow of blood through the kidneys might be diminished by constructing an artificial opening between the renal artery and the renal vein so that part of the arterial blood would be diverted into the vein without passing through the kidney.

Since Carrel published his description [2] of a uniformly satisfactory technic for making a vascular anastomosis, studies of the effects of experimentally produced arteriovenous fistulas have been reported by many authors. Two instances of this lesion between the renal vessels in human subjects have been reported,[3] but we have been unable to find any recorded observations of a similar condition in the experimental animal. We therefore contribute a study of the technic required to anastomose these vessels successfully and of certain of the pathologic and physiologic effects of the lesion on the kidney and on the organism as a whole.

1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. 59:347, 1934.

2. Carrel, A.: La technique opératoire des anastomoses vasculaires et de la transplantation des viscères, Lyon méd. 93:859, 1902; The Surgery of Blood Vessels, Bull. Johns Hopkins Hosp. 18:18, 1907.

3. Varela, M. E.: Aneurisma arterio venoso de las vasos renales y asistolia consecutiva, Rev. méd. latino-am. 157:3244, 1928. Camp, F. B.: Personal communication to the authors.

METHODS

Carotid loops [4] were constructed in male dogs of varying sizes, and after a series of daily observations had been made to establish the average normal systolic blood pressure and pulse rate an arteriovenous fistula was created between the renal vessels. Daily determinations of the urea nitrogen content of the blood gave an indication of the functional ability of the renal substance distal to these communications.

Recent publications on surgical management of the blood vessels stress the necessity of approximating the intima of one vessel to that of the other. The methods of accomplishing this are well known. Of almost equal importance is the exclusion of blood and tissue juices from the immediate field of operation. That adequate exposure of the vessels must be secured is obvious. The procedure to be described fulfils these requirements.

The dog, anesthetized with pentobarbital sodium given intravenously, is placed on the table on its side, with a large sand bag under the dependent lumbar region. The skin of the entire flank is shaved and prepared in the usual manner, and a rectangular field just below and parallel to the last rib is draped with sterile towels. The incision should be 9 to 10 cm. long and is made parallel to the last rib and about 2 cm. below it. When the right renal vessels are to be exposed, the rib is resected subperiosteally from its angle to the costal cartilage. This is not necessary on the left side. The original incision is carried through the oblique and transversus muscles and their fused tendons posteriorly. The parietal peritoneum is pushed forward and the perirenal space entered. The renal fascia is incised, and the kidney is freed from its bed by blunt dissection and delivered into the wound. The peritoneum is gently peeled from the anterior surface of the kidney and its pedicle, and the wound is lined with moist Mikulicz pads. With the kidney tilted forward toward the dog's abdomen, the posterior aspect of the vessels may be freed from all other structures. The kidney is then tilted toward the animal's back, and the remaining surfaces of the artery and vein are dissected free. A Beard lid clamp with rubber-shod tips is loosely applied to both artery and vein as close to the vena cava as possible. At the hilus the vessels are occluded by means of a flexible-tipped, rubber-shod artery forceps (fig. 1). The clamps must not be so tightly applied as to injure seriously the walls of the artery or vein. With the posterior aspect of the vessels in view, all other structures are packed out of the way with strips of silk cloth soaked in a solution of 3 parts petrolatum and 1 part liquid petrolatum.

With a curved bistoury a longitudinal incision is made into the wall of the vein which is apposed to the artery, and the incision is lengthened to the desired size with small sharp scissors. The lumen is immediately washed with saline solution at 40 C. An incision the mirror image of this is now made in the artery, and with tiny toothed forceps and a knife the adventitia is stripped back from the edges of the opening. Both wounds are lightly coated with a warm solution of petrolatum and mineral oil. With Deknatel's finest arterial silk soaked in petrolatum and threaded on Kalt's smallest curved corneal needles, stay sutures are so placed and tied (fig. 1) as to bring the ends of the venous and arterial defects together. With the aid of a temporary tension suture midway between the stay sutures (fig. 2) the long end of one of the latter is used as a running stitch to

4. Child, C. G., and Glenn, F.: Modification of Van Leersum Carotid Loop for Determination of Systolic Blood Pressure in Dogs, Arch. Surg. **36**:381 (March) 1938.

approximate the posterior walls of the artery and the vein. When the suture line is completed, the silk is tied to the short end of the second stay suture, and the position of the kidney is reversed so as to bring the anterior aspect of the vessels into view. The strips of silk cloth are rearranged, and the edges of the opening and the posterior suture line are washed with saline solution and coated with petrolatum-oil solution. The long end of the second stay suture brings the anterior walls of the vessels together in a running stitch. The closure of the

Fig. 1.—Drawing to show the exposure gained and the manner in which the clamps are placed and the vessels opened. The inset shows the method of tying the stay sutures so as to evert the edges of the artery and vein.

stoma is completed by tying this suture to the short end of the first stay suture. In placing the sutures in the vessels it is to be remembered that the smaller the everted margin the less will be the likelihood of constriction of either the artery or the vein at the site of the fistula. With sponges saturated in warm saline solution packed about the suture lines, the clamp at the hilus is removed. It is not usually necessary to deprive the kidney of its blood supply for more than thirty-five or forty minutes while the fistula is being made.
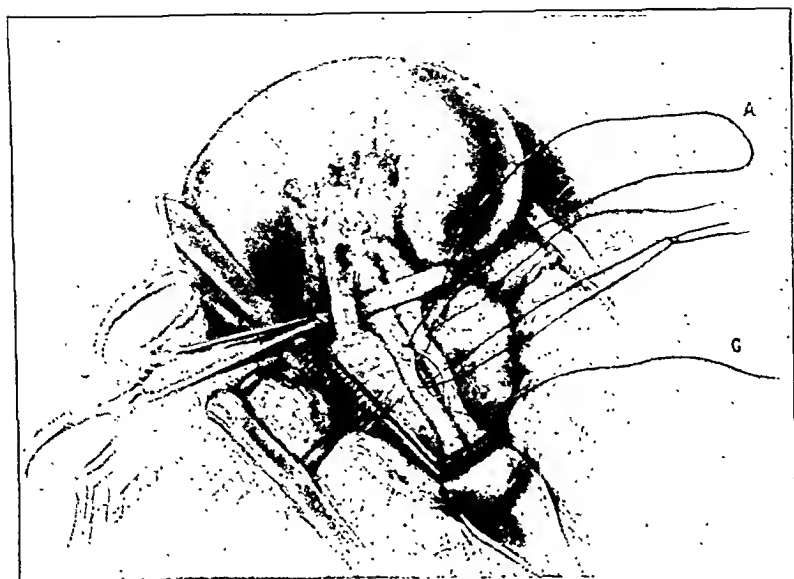
Fig. 2.—Opposite side of the pedicle from that seen in figure 1, showing the completed posterior suture line and the position of the temporary tension suture.
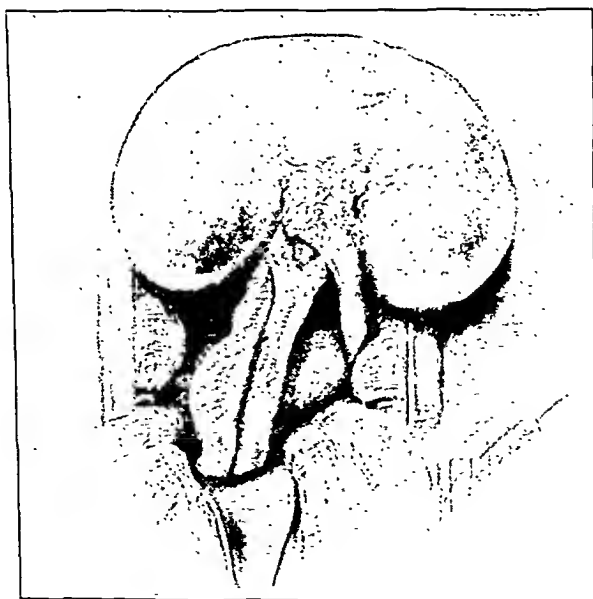
Fig. 3.—Completed anastomosis. The distention of the vein at the fistula is apparent. There is no constriction of the vessels due to suturing.

The downward rush of blood forces out between the sutures the small amount of air that may have been enclosed within the vessels. The Beard clamp is then removed, and within a few seconds the kidney assumes a lighter hue, though it never regains its original color. After a few minutes the packs are removed and the anastomosis inspected. The churning of arterial blood within the distended vein is clearly apparent (fig. 3), and a strong thrill can be felt over the vessels and the hilus of the kidney. The kidney is then replaced, with care not to kink the pedicle, and the operation is completed by closing the wound in layers with interrupted sutures of silk in the muscles and running intracutaneous or interrupted sutures in the skin. A simple collodion-gauze dressing is applied over the operative field.

In this manner artificial communications between the renal artery and the renal vein have been fashioned in 12 dogs, and all but 1 (experiment 9) of the fistulas have remained patent throughout the period of observation. The average length of the fistula, as measured at the time of operation, was 1 cm. In 2 dogs (experiments 5 and 7) with larger fistulas a thrill was felt over the flank, and in all instances in which the fistula was patent a bruit was audible.
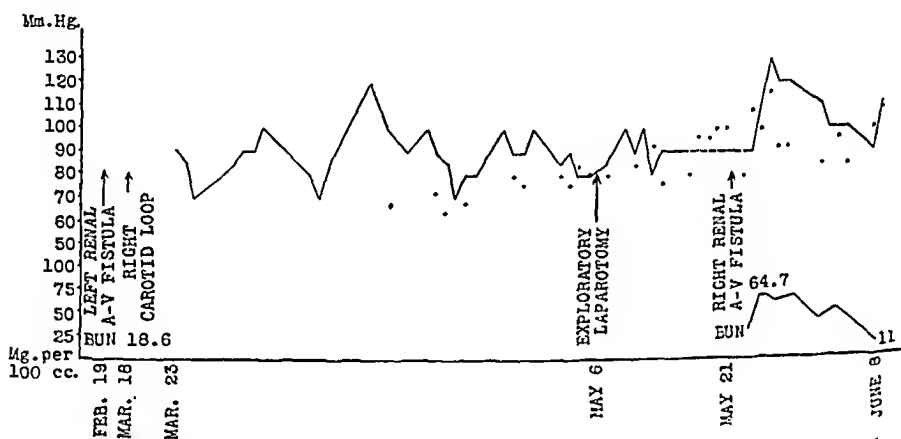
Fig. 4 (experiment 1).—Transient rise in the pulse, blood pressure and urea nitrogen content of the blood after the formation of the second fistula. (As in the three following figures the lower line represents the level of the urea nitrogen. The upper line is a graph of the systolic blood pressure. The circles represent the pulse rate.)

Detailed protocols of the experiments are here presented. Protocols in tabulated form, together with pathologic reports, will be found at the end of the article.

PROTOCOLS

Experiment 1.—In a male dog weighing 26½ pounds (12.2 Kg.) a left renal arteriovenous fistula 8 mm. long was made on Feb. 19, 1938. On Feb. 21 the urea nitrogen content of the blood was 18.6 mg. per hundred cubic centimeters. A right carotid loop was fashioned on March 18, and between March 23 and May 20 the average daily blood pressure was 95 and the pulse rate 80. An exploratory laparotomy on May 6 revealed the fistula to be patent. On May 21 an arteriovenous fistula 9 mm. long was made in the right kidney. The blood pressure rose to 130 by the fourth postoperative day, and the pulse rate to 116 (fig. 4). The urea nitrogen content of the blood rose gradually to 64.7 by the third postoperative

day and remained approximately at this level for ten days. The blood pressure had fallen to 100 and the pulse rate to 96 by the twelfth postoperative day and have remained at these levels to the present time. The value for urea nitrogen on the seventeenth postoperative day was 11 mg. The dog is alive and well. A bruit can be heard over each flank.

Experiment 2.—In a male dog weighing 30 pounds (13.6 Kg.) a left renal arteriovenous fistula 1 cm. long was made on Feb. 7, 1938. Four days later a right carotid loop was fashioned, and from February 17 to February 28 the average daily blood pressure was 100. The value for urea nitrogen on February 14 was 17 mg. An arteriovenous fistula 1 cm. long was made in the left kidney February 28, and uremia developed, proving fatal on March 4. The blood pressure was 160 during the first two postoperative days and 145 the day before death. The value for urea nitrogen rose rapidly and was 136 on the morning of the day on which the animal died.

Fig. 5 (experiment 2).—Right kidney twenty-five days after formation of a renal arteriovenous fistula. The organ is very small and is composed of islets of pale necrotic material containing calcium separated by bands of fibrous tissue and fat. A bristle lies in the communication between the vessels.

Experiment 3.—In a male dog weighing 31 pounds (14.1 Kg.) a right renal arteriovenous fistula 1 cm. long was made on Feb. 18, 1938. After the formation of a right carotid loop on February 25, the animal's blood pressure on March 7 was found to be 150 and the urea nitrogen content of the blood 19.4 mg. per hundred cubic centimeters. After a right nephrectomy on March 7 the dog had uremia and died in four days. The blood pressure was 170 on the third postoperative day but did not rise above 140 on the other days. The value for urea nitrogen rose progressively, reaching 162.3 mg. per hundred cubic centimeters about six hours before death (fig. 6).

Experiment 4.—In a male dog weighing 36 pounds (16.3 Kg.) a right carotid loop was constructed on March 8, 1938, and between March 12 and March 19 the average daily blood pressure was 120. A right renal arteriovenous fistula 1 cm.

long was made on March 19, and for three days thereafter there was a slight rise in the urea nitrogen content of the blood but no significant change in the blood pressure. An intravenous pyelogram on March 30 resulted in visualization of the left urinary tract only. The dog died of distemper eighteen days after the formation of the fistula. The opening was patent and measured 4 mm. in diameter.

Experiment 5.—In a male dog weighing 41½ pounds (19 Kg.) a right carotid loop was fashioned on March 21, 1938. The average daily blood pressure between March 26 and April 2 was 110, and an intravenous pyelogram on March 30 was effective in visualizing the urinary tract on both sides. A right renal arteriovenous fistula 1.2 cm. long was made on April 2. No elevation of blood pressure or of the urea nitrogen content of the blood followed this, and on April 20 an arteriovenous fistula 1.8 cm. long was made in the left kidney. An intravenous pyelogram
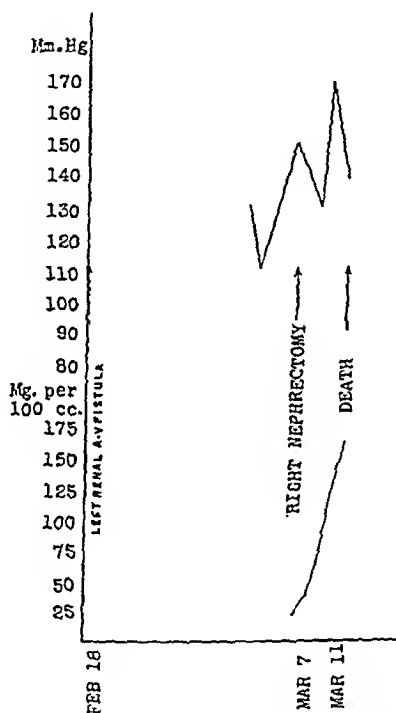
Fig. 6 (experiment 3).—The removal of the normal kidney opposite to the side on which a renal arteriovenous fistula has been made is shown to result in a progressive increase in the urea nitrogen content of the blood and a slight transient rise in the systolic blood pressure.

the next day did not visualize the urinary tract on either side. The dog's blood pressure rose gradually, as did the pulse rate, the former being 150 on March 23 and the latter 96. The animal died of uremia, with a urea nitrogen content of the blood of 204.5 mg. per hundred cubic centimeters on the fifth postoperative day.

Experiment 6.—In a male dog weighing 40 pounds (18.1 Kg.) a right carotid loop was made on March 21, 1938, and the average daily blood pressure between March 28 and April 8 was 110. An intravenous pyelogram on March 30 successfully visualized both urinary tracts. On April 8 a right renal arteriovenous fistula 2 cm. long was made. This was followed by a slight rise in the urea nitrogen of the blood and the pulse rate and a fall in the blood pressure, the respective levels of the blood and the pulse rate and a fall in the blood pressure, the respective levels being 22.4 mg., 140 and 90. Bilateral cutaneous ureterostomies were formed on April 15, and on the following day catheters were inserted and a differential phenol

sulfonphthalein test done, showing 10 per cent less excretion of the dye on the right in one hour. The right kidney excreted 18 cc. of urine in forty-three minutes and the left 36 cc. That excreted on the right contained 0.82 Gm. of urea nitrogen per liter and that on the left 9.3 Gm. Three days later the animal succumbed to bilateral pyelonephritis. The value for urea nitrogen on April 18 was 109 mg. per hundred cubic centimeters of blood.

Experiment 7.—In a male dog weighing 46 pounds (20.9 Kg.) a right carotid loop was constructed on March 22, 1938. An intravenous pyelogram on March 30 was effective in visualizing both urinary tracts. The average daily blood pressure between March 31 and April 8 was 100. A right renal arteriovenous fistula 1.5 cm. long was made on April 9, and two days later the urea nitrogen content of the blood was 17.3 mg. per hundred cubic centimeters, the blood pressure 110 and
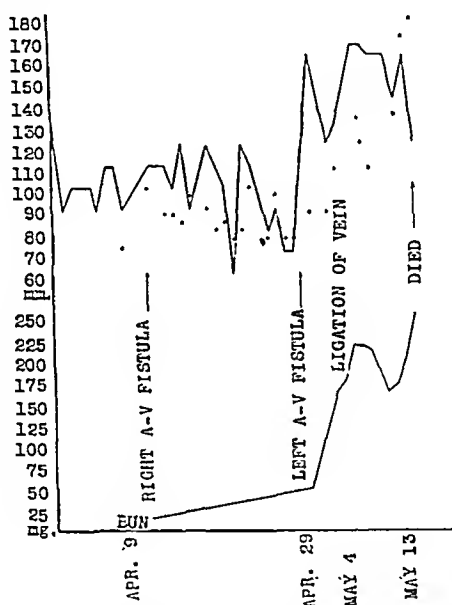
Fig. 7 (experiment 7).—Chart showing the manner in which the mild hypertension produced by the formation of the second fistula is accompanied by a rise in the pulse rate and the urea nitrogen content of the blood. A transient decrease in the last followed the ligation of the left renal vein between the fistula and the vena cava.

the pulse rate 100. An intravenous pyelogram on April 21 effected visualization on the left side only. On April 29 a left renal arteriovenous fistula 7 mm. long was made. The changes which followed this are clearly shown in figure 9. Thirteen days after the formation of the second fistula the animal died in uremia, the urea nitrogen content of the blood being 252.4 mg. per hundred cubic centimeters.

Experiment 8.—In a male dog weighing 42 pounds (19.1 Kg.) a right carotid loop was fashioned on March 21, 1938, and daily determinations of the blood pressure between April 7 and April 25 established an average level of 110. An intravenous pyelogram on April 21 visualized both urinary tracts. On April 24 a right renal arteriovenous fistula 1.2 cm. long was made, and a rise of the blood pressure to 160 appeared in two days, though the value for urea nitrogen was

only 19.9 mg. per hundred cubic centimeters. The construction of a left renal arteriovenous fistula 8 mm. in length on May 6 was followed by a further rise in blood pressure to a peak of 205 on the sixth postoperative day. After the formation of the first fistula the pulse rate did not vary significantly from an average of 100. The dog died in a uremic convulsion (value for nitrogen, 266.4 mg. per hundred cubic centimeters of blood) seven days after the second fistula was established.

Experiment 9.—In a male dog weighing 31½ pounds (14.2 Kg.) a right carotid loop was constructed on March 25, 1938. The average daily blood pressure between March 31 and April 9 was 90. On April 29 a right renal arteriovenous fistula 1 cm. long was made. A transient rise in blood pressure, reaching a peak of 160 on the fourth postoperative day, appeared after this, but only a slight rise in pulse rate occurred, and the value for urea nitrogen in the blood on May 2 was

Fig. 8 (experiment 8).—Right kidney eighteen days after formation of a renal arteriovenous fistula. The organ is slightly reduced in size. The cortex is pinkish yellow, the medulla light yellow and the region of the arcuate vessels dark red.

14.9 mg. per hundred cubic centimeters. After May 26 a bruit could not be heard, and since no permanent change in the vital signs had been produced the animal was killed by means of an overdose of chloroform on June 16.

Experiment 10.—In a male dog weighing 41 pounds (18.6 Kg.) a right carotid loop was fashioned on May 14, 1938. The average daily blood pressure between May 19 and June 2 was 100 and the pulse 72. On June 2 a right renal arteriovenous fistula 11 mm. long was made. This was followed by transient tachycardia but by no change in the systolic tension. Fourteen days later the animal was killed and the aorta injected with Hill's solution.[5] A rich collateral circulation was revealed, arising chiefly from the right ureteral, spermatic and lowest intercostal vessels.

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5. Hill, E. C.: Notes on an Opaque X-Ray Mass, Bull. Johns Hopkins Hosp. **35**:218, 1924.

Experiment 11.—In a male dog weighing 37½ pounds (17 Kg.) a right carotid loop was made on April 22, 1938.   The average daily blood pressure between April 29 and May 20 was 120 and the pulse rate 70.   The establishment of a right renal arteriovenous fistula 1 cm. long on May 24 was followed by a slight
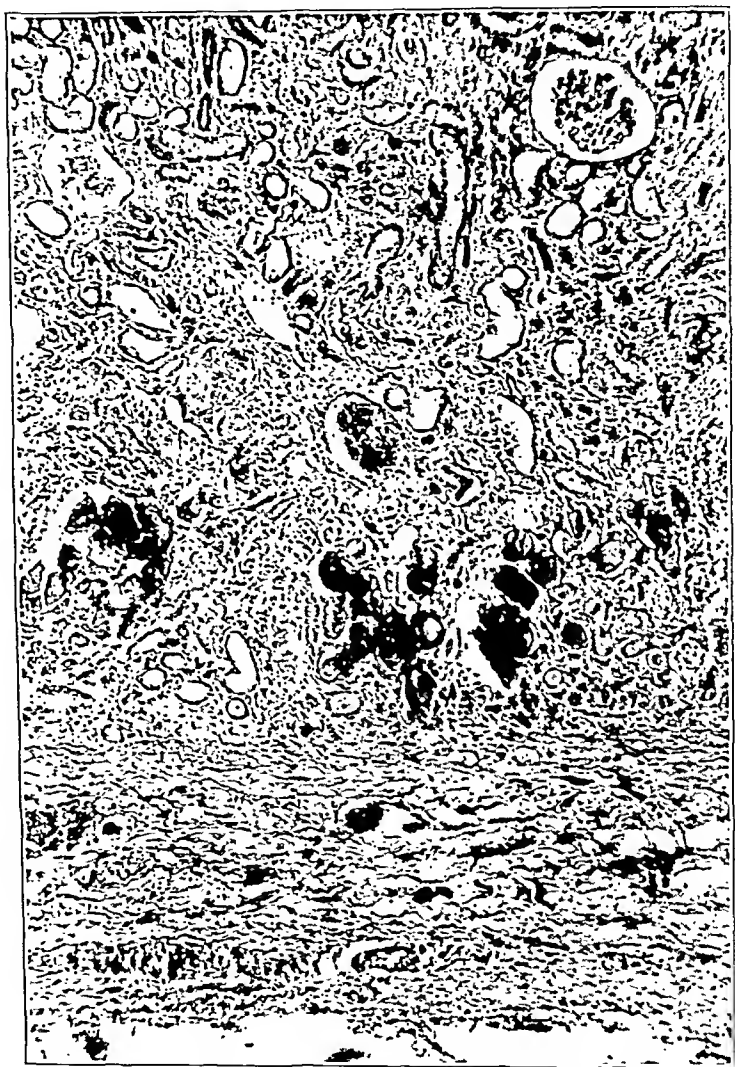
Fig. 9 (experiment 8).—Right kidney eighteen days after formation of a renal arteriovenous fistula.   (For gross picture see figure 4.)   The dilated capsular and perinephric vessels are well seen.   There is diffuse cortical interstitial fibrosis. The various types of tubular change are apparent, and the deposition of calcium within the lumens of necrotic tubules is marked by the deeply stained masses near the capsule.

persistent rise in the pulse rate but no significant elevation of the systolic blood pressure. The animal is alive and well at the time of writing, and a loud bruit can be heard over the right flank.

Experiment 12.—In a male dog weighing 33 pounds (15 Kg.) a right carotid loop was fashioned on April 22, 1938, and between April 26 and May 16 the average daily blood pressure was 90. On May 16 a right renal arteriovenous fistula 1.8 cm. long was made, and a silver wire band was placed around the artery proximal to this. A slight transient rise in blood pressure, pulse rate and the urea nitrogen content of the blood appeared during the first four postoperative days, and on May 20 the silver wire band was constricted until only a slight thrill could be felt over the fistula. The right kidney was then removed. No change in the vital signs has appeared, and the dog is alive and well at the present time. A faint bruit can be heard at one point in the right flank.

<div align="center">COMMENT</div>

Pathology.—The kidney distal to an arteriovenous fistula between its vessels rapidly undergoes a series of changes which culminate in entire replacement of the organ by dense fibrous tissue and calcium. For two to four days after the formation of the fistula the organ is enlarged, deep reddish purple and obviously intensely congested. This impression is corroborated by histologic study, which reveals engorgement of all the smaller vessels with numerous diffuse interstitial hemorrhages. A varying amount of parenchymal damage is evident, but tubular changes are always seen and usually consist in granular swelling of the epithelial cells of all parts, with desquamation of many of the cells of the descending limbs of Henle's loops and of the proximal convoluted tubules.

About six days after the formation of the fistula the kidney becomes pale and begins to decrease in size in spite of the presence of many small collateral vessels which now become evident in the rather thickened perinephric tissues. On section the parenchyma is pale yellow, but the usual markings can be discerned. There is a well defined area of red about the course of the arcuate vessels between the cortex and the medulla (fig. 8). During the earlier part of this period the organ is firm, but as dissolution of the renal elements progresses the tissues become soft, and small granules of gritty material can be felt in the outer cortex. The histologic picture eighteen days after the formation of the fistula (fig. 9) shows numerous small engorged collateral vessels within the thickened capsular tissues. There is diffuse interstitial fibrosis. The tubular changes noted earlier have proceeded either to necrosis of the structure or to one of various stages of reconstruction and healing. Those tubules or parts thereof which die are, when located near the periphery of the cortex, represented by plugs of acidophilic material containing basophilic granules which take the von Kossa stain and appear to be calcium.

Between the twentieth and thirtieth days the kidney undergoes anemic necrosis, which usually involves the entire organ, though a few renal elements about the pelvis and the arcuate vessels and just beneath the capsule may survive for a longer time. The organ is about half the normal size and is embedded in dense, rather vascular fibrous tissue. The parenchyma is pale yellow, and the usual markings are absent. The cortex, the medulla and many of the pyramids are separated by wide bands of pale fibrous tissue and fat (fig. 5). Between these are islands of caseous material containing varying amounts of calcium. A section taken at this time and viewed under the microscope reveals the "ghosts" of the renal structures infiltrated with young fibrous tissue and a few inflammatory cells, most of which are mononuclear. Dilated collateral vessels are no longer so greatly in evidence.

Pathologic Physiology.—In Holman's recent monograph [6] the general circulatory changes known to follow the establishment of an arteriovenous fistula of adequate size have been discussed. Undoubtedly certain of these changes affected the hemodynamics in this series of animals. We did not, however, observe any increase in pulse rate after the formation of one fistula or of bilateral fistulas which could not be attributed to another and more probable cause. Studies of the blood volume and cardiac output were not made. We did not find definite evidence of cardiac hypertrophy. It is probable that our failure to note any of the significant clinical or postmortem signs usually found in the presence of an arteriovenous fistula was due to the small caliber of the openings and the short periods of observation.

The local circulatory changes induced by the formation of a fistula between the renal vessels are similar to those appearing about any physiologically significant [7] communication of this nature. The exact mechanism which stimulates the formation of an extensive collateral blood supply to the structure distal to the short circuit is not completely understood. It is of interest to note that after the kidney is functionally useless the rich anastomotic supply becomes progressively less abundant.

In dogs between 30 and 45 pounds in weight the formation of an arteriovenous fistula greater in length than 9 mm. diverts a part of the renal blood supply sufficient eventually to inhibit completely the excretory utility of the kidney.

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6. Holman, E.: Arteriovenous Aneurysm: Abnormal Communications Between the Arterial and Venous Circulations, New York, The Macmillan Company, 1937.

7. Clark, E. R., and Clark, E. L.: Observations on the Living Preformed Blood Vessels as Seen in a Transparent Chamber Inserted in the Rabbit's Ear, Am. J. Anat. **49**:441, 1932.

If bilateral fistulas of adequate size are established (experiments 2, 5, 7 and 8), or if the normal kidney opposite to that in which a fistula is present is removed (experiment 3, fig. 6), the dog dies in uremia in four to seven days. However, small amounts of dilute urine may be excreted during the early postoperative period, and in experiment 6 it was found that urine containing a diminished amount of urea was excreted as late as eight days after the formation of a fistula between the main vessels of the kidney.

Intravenous pyelograms taken at two, fifteen and thirty-five minutes in experiments 4, 5, 6 and 7 and a differential phenolsulfonphthalein test in experiment 6 demonstrate the inability of the kidney beyond the lesion to excrete either the diodrast or the dye in concentrations equal to those obtained from normal kidneys.

Since, however, the construction of small bilateral fistulas (experiment 1, fig. 4) does not result in fatal uremia, we believe that the chief handicap to renal function in this condition is the lack of circulation of an adequate amount of blood through the organ. This impression is confirmed by the fact that ligation of the renal vein between a large arteriovenous fistula and the vena cava (experiment 7, fig. 7) resulted in a transient fall in an otherwise progressive rise of the level of urea nitrogen in the blood. This effect was presumably due to a temporary increase in the renal blood flow.

The aforementioned changes seem to indicate that a renal arteriovenous fistula renders the involved kidney ischemic. This method of producing ischemia is different from those heretofore reported, and only a mild degree of hypertension is produced (protocols and figs. 4 and 7). Constriction of the renal arteries,[1] ligation of the ureters[8] or compression of the kidneys with ribbon gut[9] results in severe systemic hypertension. Blalock[10] has offered good evidence that the hypertension produced by ligation of the ureters is in reality secondary to renal ischemia. Similarly, it is probable that direct compression of the kidney is effective in causing a rise in arterial tension, because by this means the renal blood flow is diminished. Complete occlusion of the renal arteries in the presence of an adequate collateral circulation is effective in pro-

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8. Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Changes in Blood-Pressure in Relation to Experimental Renal Insufficiency, Tr. A. Am. Physicians **51**:280, 1936. Levy, S. E.; Mason, M. F.; Harrison, T. R., and Blalock, A.: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, Surgery **1**:238, 1937.

9. Glenn, F., and Lasher, E. P.: Unpublished data.

10. Levy, S. E.; Light, R. A., and Blalock, A.: The Blood Flow and Oxygen Consumption of the Kidney in Experimental Renal Hypertension, Am. J. Physiol. **122**:38, 1938.

ducing a well sustained increase in tension.[11]   One would therefore expect the severe renal ischemia distal to an arteriovenous fistula to be sufficient to produce a similar result.

There is, however, at least one apparent difference between the circulation distal to a Goldblatt clamp and that beyond an arteriovenous fistula.   Though in either instance there is a diminution in the arterial pressure, a rise in venous pressure within the renal vein after the application of a Goldblatt clamp to the artery has not been demonstrated. This rise is known to occur distal to an arteriovenous fistula.[12]   That the level of venous pressure may be significant is indicated both by these experiments and by studies reported several years ago [13] in which it was found that constriction of the renal vein produced a mild systemic hypertension in no way so great as that which follows partial occlusion of the renal artery.

It is our impression, therefore, that a high venous pressure within the kidney may inhibit significantly the formation or dissemination of the "effective substance" hypothecated by Goldblatt.   Recently published experiments by Blalock and Levy [14] would tend to refute this, but sufficient data are not given in their report.

SUMMARY

1. A satisfactory technic for the production of an arteriovenous fistula between the renal vessels of the dog is described.

2. Certain of the pathologic changes observed in and about the kidney distal to such a lesion are pointed out.

3. A few of the physiologic changes appearing subsequent to the formation of this type of fistula are discussed in relation to: (*a*) general circulatory dynamics; (*b*) local circulatory changes; (*c*) kidney function, and (*d*) renal ischemia.

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12. Ney, E.: Ueber die Bedeutung der Venen bei arteriovenösen Aneurysmen, Arch. f. klin. Chir. **100:**531, 1912-1913.

13. Bell, E. T., and Pedersen, A. H.: The Causes of Hypertension, Ann. Int. Med. **4:**227, 1930. Pedersen, A. H.: A Method of Producing Experimental Chronic Hypertension in the Rabbit, Arch. Path. **3:**912 (May) 1927. Menendez, E. B.: Stase veinuse du rein normal au énervé et hypertension artérielle, Compt. rend. Soc. de biol. **113:**461, 1933.

14. Levy, S. E., and Blalock, A.: Experimental Attempts to Prevent or Abolish the Hypertension That Is Associated with Renal Ischemia, Surgery **3:** 899, 1938.

PROTOCOLS AND PATHOLOGIC REPORTS

In the following tabulations, A-V signifies arteriovenous; B.U.N., urea nitrogen content of the blood; B.P., blood pressure; P., pulse rate.

PROTOCOL

Experiment 1: Subject, male dog weighing 26½ pounds (12.2 Kg.)

Feb. 19, 1938	Left renal A-V fistula 8 mm. long
Feb. 21	B.U.N. 18.6
March 18	Right carotid loop
March 23–May 5	Average daily B.P. 95 P. 80
May 6	Exploratory laparotomy; fistula patent
May 7–May 20	Average daily B.P. 95 P. 94
May 21	Right renal A-V fistula 9 mm. long
May 22	B.P. 90 P. 80
May 23	B.U.N. 30.7 B.P. 90 P. 108
May 24	B.U.N. 64.7 B.P. 110 P. 100
May 25	B.U.N. 64.3 B.P. 130 P. 116
May 26	B.U.N. 62.9 B.P. 120 P. 92
May 27	B.U.N. 63.8 B.P. 120 P. 92
May 28	B.U.N. 64.3
May 31	B.U.N. 40.5 B.P. 110 P. 84
June 2	B.U.N. 50.7 B.P. 100 P. 96
June 7	B.U.N. 11.0 B.P. 100 P. 96

At the time of writing the animal is still alive, and both fistulas are patent.

PROTOCOL

Experiment 2: Subject, male dog weighing 30 pounds (13.6 Kg.).

Feb. 7, 1938	Right renal A-V fistula 1 cm. long
Feb. 11	Right carotid loop
Feb. 14	B.U.N. 17.0
Feb. 17–Feb. 28	Average daily B.P. 100
Feb. 28	Left renal A-V fistula 1 cm. long
March 1	B.P. 160
March 2	B.U.N. 69.9 B.P. 160
March 3	B.U.N. 139.8 B.P. 145
March 4	B.U.N. 136
March 4	(fourth postoperative day) Dog died with uremia

PATHOLOGIC PICTURE

Gross.—The right kidney was approximately one-third the normal size. It was represented by islets of homogeneous yellow tissue separated by bands of fibrous tissue containing fat. The capsule was extremely adherent. Collateral vessels were rather numerous but were small.

The left kidney was deep reddish purple and slightly larger than normal. The capsule stripped easily, leaving a smooth surface. On section the parenchymal markings were somewhat obscured, owing to the dark color. The peripheral 3 to 4 mm. of the cortex was light yellowish red. A deep red band marked the corticomedullary junction.

Microscopic.—The mass representing the right kidney was composed of granular acidophilic débris containing numerous basophilic granules. Interspersed between these were wide bands of dense fibrous tissue infiltrated with large mononuclear

cells and lymphocytes. The large veins presented greatly thickened walls. The arteries were not remarkable.

Section of the left kidney showed extreme engorgement of all the small vessels, with numerous scattered areas of hemorrhage in both the cortex and the medulla. There was evidence of extensive tubular damage, most marked in the descending loops of Henle and in the proximal convoluted tubules. The glomerular tufts were in most instances bloodless. There were a few red cells in many of the capsules of Bowman.

PROTOCOL

Experiment 3. Subject, a male dog weighing 31 pounds (14 Kg.).

Feb. 18, 1938	Left renal A-V fistula 1 cm. long
Feb. 25	Right carotid loop
March 7	B.U.N. 19.4 B.P. 150
March 7	Right nephrectomy
March 8	B.U.N. 37.2 B.P. 140
March 9	B.U.N. 61.2 B.P. 130
March 10	B.U.N. 119.0 B.P. 170
March 11	B.U.N. 162.3 B.P. 140
March 11 (fourth postoperative day) Dog died with uremia	

PATHOLOGIC PICTURE

Gross.—The left kidney was about half the size of the one removed at operation. It was embedded in a thickened capsule containing vessels of a well established collateral circulation. The capsule stripped easily, leaving a smooth surface. On section the parenchyma was pale and its markings somewhat indistinct.

Microscopic.—Section of the left kidney showed engorgement of the small vessels in the cortex, with a few small areas of interstitial hemorrhage. The capillary loops of the glomeruli were poorly filled with blood. The capsules of Bowman were dilated. There was good preservation of the anatomic markings of the tubules in both cortex and medulla.

PROTOCOL

Experiment 4. Subject, male dog weighing 36 pounds (16.3 Kg.).

March 8, 1938	Right carotid loop
March 12-March 19	Average daily B.P. 120
March 19	Right renal A-V fistula 1 cm. long
March 21	B.U.N. 35.9 B.P. 120
March 22	B.U.N. 20.3 B.P. 120
March 23	B.U.N. 16.7 B.P. 100
March 25	B.U.N. 16.2 B.P. 100
March 30	Intravenous pyelogram; visualization on left only
April 6 (eighteenth postoperative day) Dog died of distemper	

PATHOLOGIC PICTURE

Gross.—The left kidney was apparently normal. The right kidney was slightly larger than the left. The capsule was thickened and contained numerous dilated vessels. On section the parenchyma was mottled yellow and red. The usual markings were indistinct. The corticomedullary junction was marked by an irregular purple band. The medulla was yellowish white and soft.

Microscopic.—Section of the right kidney showed a picture very similar to that described in the right kidney in experiment 5, though calcium deposition was more plentiful in the present instance. Section of the left kidney showed no significant pathologic changes.

<div align="center">PROTOCOL</div>

Experiment 5. Subject, male dog weighing 41½ pounds (19 Kg.).

March 21, 1938	Right carotid loop
March 26-April 2	Average daily B.P. 110
March 30	Intravenous pyelogram; bilateral visualization
April 2	Right renal A-V fistula 1.2 cm. long
April 4	B.U.N. 16.3 B.P. 120 P. 118
April 11	B.U.N. 18.2 B.P. 110 P. 80
April 20	Left renal A-V fistula 1.8 cm. long
April 21	Intravenous pyelogram; no visualization
April 21	B.U.N. 71.7 B.P. 110 P. 80
April 22	B.U.N. 117.4 B.P. 120 P. 92
April 23	B.U.N. 157.9 B.P. 150 P. 96
April 25	B.U.N. 204.5
April 25 (fifth postoperative day)	Dog died of uremia

<div align="center">PATHOLOGIC PICTURE</div>

Gross.—The left kidney was approximately four times normal size. Its peritoneal surface was lightly adherent to the omentum and to an adjacent loop of small bowel. The parenchyma was deep purplish red. The capsule stripped easily, leaving a smooth friable surface. On section the parenchymal markings were indistinct. There were a few scattered light yellow areas, suggesting early anemic necrosis.

The right kidney was pale yellow and was less than one-half the normal size. The surrounding tissues were thickened and contained numerous dilated anastomotic vessels. On section the parenchyma was yellow throughout, and broad bands of gray fibrous tissue were evident. There were scattered islets of yellowish soft material in the more peripheral part of the organ.

Microscopic.—Section of the right kidney showed the changes of anemic necrosis in almost the entire organ. A few glomerular and tubular elements were preserved about the arcuate vessels and were embedded in dense fibrous tissue. The left kidney presented the changes of early anemic necrosis and infiltration with a few polymorphonuclear and mononuclear leukocytes. There was extensive interstitial hemorrhage, more marked in the medulla.

<div align="center">PROTOCOL</div>

Experiment 6. Subject, male dog weighing 40 pounds (18.1 Kg.).

March 21, 1938	Right carotid loop
March 28-April 8	Average daily B.P. 110
March 30	Intravenous pyelogram; bilateral visualization
April 8	Right renal A-V fistula 2 cm. long
April 9	B.P. 110 P. 132
April 11	B.U.N. 22.4 B.P. 90 P. 140
April 15	Bilateral cutaneous ureterostomies

April 16	Catheters inserted and differential phenolsulfonphthalein test done, showing 10 per cent less excretion of dye on the right in one hour. The right kidney excreted 18 cc. of urine in forty-three minutes and the left 36 cc. That excreted on the right contained 0.820 Gm. of urea nitrogen per liter and that on the left 9.3 Gm.
April 18	B.U.N. 109
April 19	Dog died of bilateral pyelonephritis

PATHOLOGIC PICTURE

Gross.—Both kidneys were almost completely destroyed by infection, the tissue being soft, friable and dark red.

PROTOCOL

Experiment 7. Subject, male dog weighing 46 pounds (20.9 Kg.).

March 22, 1938	Right carotid loop
March 30	Intravenous pyelogram; bilateral visualization
March 31-April 8	Average daily B.P. 100
April 9	Right renal A-V fistula 1.5 cm. long
April 11	B.U.N. 17.3 B.P. 110 P. 100
April 21	Intravenous pyelogram; visualization on left only
April 29	Left renal A-V fistula 7 mm. long
April 30	B.U.N. 49.3 B.P. 160 P. 88
May 2	B.U.N. 127.2 B.P. 120 P. 88
May 3	B.U.N. 159.3 B.P. 130 P. 108
May 4	Ligation renal vein at vena cava; ether anesthesia
May 4	B.U.N. 174.7
May 5	B.U.N. 214.3 B.P. 165 P. 116
May 6	B.U.N. 217.0 B.P. 165 P. 120
May 7	B.U.N. 211.5 B.P. 160 P. 108
May 9	B.U.N. 161.7 B.P. 160 P. 124
May 10	B.U.N. 172.4 B.P. 140 P. 132
May 11	B.U.N. 201.7 B.P. 160 P. 168
May 12	B.U.N. 252.4 B.P. 120 P. 176

May 12 (thirteenth postoperative day) Dog died of uremia

PATHOLOGIC PICTURE

Gross.—The left kidney was deep purple but approximately normal in size. The perirenal tissues were slightly indurated and contained a few small areas of diffuse hemorrhage. The capsule stripped easily, leaving a smooth surface. Several dilated collateral capsular vessels were present. On section the parenchyma presented no striking changes except those of congestion.

The right kidney was slightly smaller than normal and was embedded in thickened fibrous tissue containing an abundant collateral circulation. In a few places the capsule was adherent to the parenchyma by delicate strands of fibrous tissue. On section the anatomic markings were present but indistinct. The medulla was bright yellow, as was an arc of tissue in the region of the arcuate vessels. The cortex was pinkish yellow and presented punctate areas which were lighter in color and contained particles of gritty material.

Microscopic.—Section of the left kidney showed changes very similar to those described for the right kidney in experiment 8. There was evidence, however, of more advanced tubular degeneration and of more extensive deposition of calcium.

<div align="center">PROTOCOL</div>

Experiment 8.   Subject, male dog weighing 42 pounds (19.1 Kg.).

March 21, 1938	Right carotid loop
April 7–April 25	Average daily B.P. 110
April 21	Intravenous pyelogram; bilateral visualization
April 24	Right renal A-V fistula 1.2 cm. long
April 26	B.P. 120 P. 108
April 27	B.P. 160 P. 104
April 28	B.U.N. 19.9 B.P. 160 P. 80
May 6	Left renal A-V fistula 8 mm. long
May 7	B.U.N. 41.0 B.P. 170 P. 72
May 9	B.U.N. 143.0 B.P. 140 P. 100
May 10	B.U.N. 152.3 B.P. 160 P. 100
May 11	B.U.N. 214.3 B.P. 200 P. 88
May 12	B.U.N. 266.4 B.P. 205 P. 100
May 13 (seventh postoperative day)	Dog died of uremic convulsion

<div align="center">PATHOLOGIC PICTURE</div>

Gross.—The left kidney was surrounded by a large area of ecchymosis. Collateral vessels were not evident. The capsular surface was smooth, and on section the parenchyma was deep purplish red. Immediately beneath the capsule were a few tiny areas of light yellow discoloration. The right kidney (fig. 4) was approximately one-half the normal size. The perirenal tissues were thickened and contained numerous dilated collaterals. The capsule stripped easily. On section the parenchyma was light pinkish yellow, and normal cortical markings could be discerned. The medulla, however, was uniformly light yellow. In the more peripheral part of the cortex were small areas of soft yellow material containing granules suggestive of calcium.

<div align="center">PROTOCOL</div>

Experiment 9.   Subject, male dog weighing 31½ pounds (14.2 Kg.).

March 25, 1938	Right carotid loop
March 31–April 9	Average daily B.P. 90
April 29	Right renal A-V fistula 1 cm. long
April 30	B.P. 90 P. 96
May 2	B.U.N. 14.9 B.P. 140 P. 92
May 3	B.P. 160 P. 84
May 4	B.P. 120 P. 84
May 5	B.P. 120 P. 76
May 6	B.P. 110 P. 76
May 9–June 15	Average daily B.P. 100 P. 72
June 16	Animal killed

<div align="center">PATHOLOGIC PICTURE</div>

Gross.—The left kidney was apparently normal. The right kidney was about one-half the size of the left, and the capsule about the hilus was thickened with scar tissue. On section the parenchyma was not remarkable except for a slight increase in fibrous tissue about the arcuate vessels and between the medullary pyramids. The site of the vascular anastomosis presented a tiny ring of scar

completely plugged by a mass of pale, partially organized fibrin which projected 1 to 2 mm. into the lumen of the vein. Neither the artery nor the vein was occluded.

<div align="center">PROTOCOL</div>

Experiment 10. Subject, male dog weighing 41 pounds (18.6 Kg.).

May 14, 1938	Right carotid loop
May 19-June 2	Average daily B.P. 100 P. 72
June 2	Right renal A-V fistula 11 mm. long
June 3	B.P. 100 P. 92
June 4-June 15	Average daily B.P. 110 P. 92
June 16 (fourteenth postoperative day)	Dog killed for injection of vessels with Hill's solution

<div align="center">PATHOLOGIC PICTURE</div>

Gross.—The left kidney was apparently normal. The right kidney was soft, light pinkish yellow and slightly larger than the left. On section the parenchymal markings were indistinct, and the entire structure resembled somewhat that of the right kidney in experiment 8 (fig. 4).

<div align="center">PROTOCOLS</div>

Experiment 11. Subject, male dog weighing 37½ pounds (17 Kg.).

April 22, 1938	Right carotid loop
April 29-May 20	Average daily B.P. 120 P. 70
May 24	Right renal A-V fistula 1 cm. long
May 25	B.P. 130 P. 100
May 31	B.P. 120 P. 92
June 1-June 16	Average daily B.P. 120 P. 100
	Animal alive and well; loud bruit present

Experiment 12. Subject, male dog weighing 33 pounds (15 Kg.).

April 22, 1938	Right carotid loop
April 26-May 16	Average daily B.P. 90
May 16	Right renal A-V fistula 1.8 cm. long
	Silver wire band placed around renal artery proximal to fistula
May 17	B.U.N. 21.4 B.P. 120 P. 84
May 18	B.P. 100 P. 112
May 19	B.P. 120 P. 124
May 20	B.U.N. 19.5
May 20	Exploratory laparotomy; silver wire band on renal artery tightened to constrict vessel so that only a slight thrill could be felt; right nephrectomy
May 21-June 16	Average daily B.P. 110 P. 104
	Animal alive and well; bruit audible

<div align="center">PATHOLOGIC PICTURE</div>

Gross.—The right kidney was deep reddish purple and slightly larger than normal. The capsule stripped easily, leaving a smooth surface. On section the parenchymal markings were fairly distinct, and the general appearance was that of moderate passive congestion of the organ.

REGENERATION OF NERVES AFTER ANASTOMOSIS OF SMALL PROXIMAL TO LARGER PERIPHERAL NERVES

AN EXPERIMENTAL STUDY CONCERNED WITH RELIEF OF PERIPHERAL NEUROGENIC PARESIS

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Recently, Dogliotti [1] recommended and attempted clinically to obtain increased innervation and function in paretic muscles supplied by a partially paralyzed nerve by means of simple section and immediate anastomosis of the involved nerve trunk. He had found experimentally that by anastomosing a portion of the proximal segment to the whole distal segment of the sciatic nerve in the dog he could demonstrate an increase in the number of nerve fibers regenerating below the point of anastomosis. This, in addition to the fact that his animals made a good functional recovery, led him to interpret his results as indicating reinnervation of muscles and a return of muscular function in excess of that originally and normally mediated by the proximal nerve fibers. If this interpretation of Dogliotti's findings is correct and if this procedure should prove practical, its value becomes obvious in the rehabilitation of patients with peripheral neurogenic paresis, such as occurs in cases of anterior poliomyelitis.

Kilvington [2] reported 4 experiments on dogs, involving in 2 instances the anastomosis of the internal popliteal nerve to the peripheral segments of both the internal and the external popliteal nerves. In the other 2 dogs the external popliteal nerve was anastomosed to the external and internal popliteal nerves. Good functional recoveries were observed

1. Dogliotti, A. M.: Etudes expérimentales et première application clinique d'une nouvelle opération destinée à augmenter et à équilibrer la fonction neuromusculaire dans la paralysis partielle des nerfs, J. de chir. 45:30-48, 1935.

2. Kilvington, B.: An Investigation on the Regeneration of Nerves, with a View to the Surgical Treatment of Certain Paralyses, Brit. M. J. 1:935-940, 1905.

in all but 1 of the animals. After recovery, electrical stimulation above the anastomosis produced contraction of both flexor and extensor muscles. Counts of the nerve fibers in proximal and distal segments of the nerves of 3 of the animals showed an increase in regenerating nerve fibers of 125, 49 and 25.4 per cent.

Kennedy[3] expressed the belief that Kilvington's results could be better evaluated by the use of the forelimb than of the hindlimb. In 2 dogs he anastomosed the proximal segments of the musculocutaneous, median and ulnar nerves (flexors) to their peripheral segments and to the musculospiral nerve. In 3 other dogs the musculospiral nerve alone (extensor) was anastomosed to the combined peripheral segments of the musculocutaneous, median, ulnar and musculospiral nerves. In the animals showing recovery, electrical stimulation of the central segments produced contractions of both flexor and extensor muscles. The same was found to be true on stimulation of the corresponding cortical centers, while stimulation of the centers associated with nerves eliminated from the anastomoses gave no response. Counts of the nerve fibers were not made.

Feiss[4] attempted anastomosis of a single proximal nerve to two peripheral nerves by what he termed a process of "fusion." This consisted of ligating the peripheral segment of one nerve to the side of another nerve with catgut after both nerves had been crushed at the point of ligation. By this method he was able to demonstrate successful regeneration from one proximal nerve to two peripheral nerves. As would be expected, the regeneration through the neuroma which formed at the site of ligature was limited, being considerably less than that which might be expected after proper end to end anastomosis of nerves. Application of this method to a human patient suffering from the paresis of poliomyelitis was attempted by Feiss,[5] without convincing results.

Anastomoses of the proximal portion of one nerve to the peripheral portions of two or more nerves in human patients, with varying degrees of success, have been reported by numerous authors. Most of these have been clinical attempts to overcome severe palsy of the facial nerve

3. Kennedy, R.: Experiments on the Restoration of Paralyzed Muscles by Means of Nerve Anastomosis: II. Anastomosis of the Nerve Supplying Limb Muscles, Phil. Tr. Roy. Soc., London, s.B **205**:27-76, 1914; abstracted, Proc. Roy. Soc., London, s.B **87**:331-335, 1914.

4. Feiss, H. O.: On the Fusion of Nerves, Quart. J. Exper. Physiol. **5**:1-30, 1912.

5. Feiss, H. O.: Recent Experimental Work on the "Fusion" of Nerves and Its Practical Bearing on Infantile Paralysis: Report of a Case of Infantile Paralysis Treated by This Method, Boston M. & S. J. **164**:667-671, 1911.

and have involved the anastomosis of the spinal accessory or the hypoglossal nerve to the facial nerve. These procedures did not involve the reinnervation of antagonistic muscles. Control studies to determine the degree of reinnervation of nerve and muscle were, of course, impossible.

Observations on the increased number of regenerating nerve fibers below the point of an anastomosis have also been made by Greenman[6] 1913, Ballerini[7] 1923, Milone[8] 1924, Nageotte[9] 1932, Purpura[10] 1930 and others. The phenomenon of luxuriant regeneration of nerves, however, is not adequate evidence for the conclusion that function is equally enhanced. An analysis of the problem reveals that certain control studies are necessary before final acceptance of such a point of view.

In the first place, it is essential to determine whether fewer, the same number or more nerve fibers regenerate after simple section and immediate anastomosis of a whole nerve trunk. Under such conditions an increased number of regenerating fibers can scarcely be interpreted as evidence for an increased innervation of muscle fibers, since presumably the original number of nerve fibers was physiologically adequate for complete innervation of all the muscles supplied by the nerve in question. Would it then follow that under the conditions described by Kilvington, Purpura, Dogliotti and others an increased number of regenerating nerve fibers necessarily implies an increased final innervation and function of the muscles supplied? In this connection Nageotte[9] wrote:

It is important to note that the number of regenerating fibers in the lower stump does not correspond with that of the afferent fibers which have traversed the cicatrix. In a lacerated wound, one may see the inferior stump of the divided nerve receive only a few neurites and nevertheless contain an almost normal number of fibers; here anatomical regeneration is good, but physiological regeneration is poor.

6. Greenman, M. J.: Studies on the Regeneration of the Peroneal Nerve of the Albino Rat: Number and Sectional Areas of Fibers; Area Relation of Axis to Sheath, J. Comp. Neurol. **23**:479-513, 1913.

7. Ballerini, M.: Sul rapporto fra il numero delle fibre rigenerate e quelle preesistenti in un nervo interrotto con la strozzatura, Gior. d. r. Accad. di med. di Torino **29**:150-157, 1923.

8. Milone, S.: Ricerche sulle consequenze dell'unione di un moncone nervoso centrale di piccolo calibro con un moncone periferico di grosso calibro, Gior. d. r. Accad. di med. di Torino **30**:50-53, 1924; Arch. per le sc. med. **47**:107-124, 1924.

9. Nageotte, J.: Sheaths of the Peripheral Nerves: Nerve Degeneration and Regeneration, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 1, sect. 5, pp. 215-231.

10. Purpura, F.: Distribuzione delle fibre nei trorchi nervosi e chirurgia dei nervi periferici, Policlinico (sez. chir.) **38**:643-652, 1931.

Secondly, it would seem essential to have control studies under conditions corresponding to those obtaining in a case of peripheral neurogenic muscular paresis. Delay in regeneration of the nerve and the fibrotic changes in nerve and muscle which follow degeneration under these conditions might result in a less satisfactory regeneration of nerve and muscle and less complete functional recovery than that found after immediate anastomoses, such as those performed by Purpura,[10] Dogliotti,[1] Gaglio and Parrinello [11] and Iovino.[12] These conditions could be approximated experimentally by delaying for a considerable period the anastomosis of the central nerve stump to a larger peripheral nerve (Kilvington procedure), the peripheral nerve having been partially paralyzed by previous section of the central stump. Furthermore, to evaluate properly this factor of delay it would be necessary to repeat the Kilvington procedure, using the same nerves and the same technic but accomplishing the anastomosis without delay.

Thirdly, the important question of whether good functional reinnervation may be obtained in one group of muscles by the use (Kilvington procedure) of nerves supplying antagonistic muscles seemed to merit further demonstration and study, particularly in connection with the control studies proposed.

With such questions in mind and to determine the practicability of this procedure the present work was undertaken.

METHODS

Operative Procedure.—Under aseptic conditions the right sciatic nerve in 4 dogs was exposed by a posterior approach in the lower portion of the thigh and the popliteal space. The common peroneal and tibial nerves were isolated, and identification was checked by the muscular response elicited by faradic stimulation of the individual nerves. Both nerves were carefully sectioned at the same level with a sharp scalpel. In 2 dogs an immediate anastomosis was performed between the proximal end of the common peroneal nerve and the distal ends of the common peroneal and tibial nerves combined. In these 2 dogs the proximal end of the tibial nerve was doubly ligated with heavy corded silk and was sutured to one side in neighboring muscles. This served (1) to check the results of Kilvington, Dogliotti and others, (2) to test the feasibility of obtaining satisfactory recovery of antagonistic muscle groups by the use of the nerve normally supplying one group only and (3) as a standard of comparison for the control experiment on 1 of the 2 remaining animals, in which the anastomosis was performed later to approximate the usual clinical conditions of prolonged partial paralysis. As a control under prolonged conditions of partial paralysis (see introductory section),

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11. Gaglio, V., and Parrinello, J.: Sulla fasciolazione e sulla sistematizzazione delle fibre nervose del radiale a dell'ulnare del cane, nel tratto omerale, Arch. ital. di anat. e istol. pat. **4**:731-750, 1933.

12. Iovino, F.: Sull'aumento numerico delle fibre dei nervi in rigenerazione, Chir. d. org. di movimento **21**:193-199, 1936.

in 1 dog the common peroneal nerve alone was cut and both ends were ligated with corded silk. One month later this dog was operated on again through a fresh incision. The ligated nerves were found, and the ends were dissected free and resected to eliminate all cicatricial tissue produced by the ligatures. The tibial nerve was next sectioned at the same level. The proximal stump of the common peroneal nerve was then anastomosed to the distal ends of the common peroneal and the tibial nerve combined. The proximal stump of the tibial nerve was ligated twice with heavy corded silk and sutured to one side in neighboring muscles.

In the fourth dog, also a control (see introductory section), the common peroneal and the tibial nerves were cut, and immediate anastomosis was performed between the proximal and distal ends of each.

In all cases end to end anastomoses were performed, three or four fine arterial silk sutures being used in the sheaths of the nerves.

Follow-up Studies.—Repeated examinations were made of all the animals, the follow-up period varying from seven to nine and one-half months. Finally, in each case the operative site was again exposed with the animal under light ether anesthesia. The operative area was examined; the condition of the anastomosis was determined, and the absence of complicating fibers from the tibial or other neighboring nerves was verified. The effects of faradic stimulation of the sciatic nerve above the anastomosis were noted, as were the effects of such stimulation of the common peroneal and the tibial nerve individually below the anastomosis.

Pathologic Preparations.—Specimens were next dissected out with care from the following points: the right sciatic nerve, the right common peroneal nerve above the anastomosis, the right common peroneal nerve and the right tibial nerve below the anastomosis. Likewise, the entire gastrocnemius and tibialis anticus muscles were dissected out on both the right and the left side in each case. The muscles were weighed, and specimens were taken from each for pathologic study. The specimens both of nerves and muscles were fixed in Zenker's solution. Cross sectional cuts of the nerves were made from paraffin blocks. These were mounted, overstained with hematoxylin and eosin, washed and counterstained with a 2 per cent effusion of crocus (Spanish saffron), according to a technic developed by Mr. William Hewitt, of the department of pathology of the University of California. Routine hematoxylin and eosin stains were done on the specimens of muscle.

Nerve Fiber Counts.—Counts of the nerve fibers, were made with the use of a microscopic carbon arc projector. Cross sectional slides of the nerve trunks were projected and magnified on a large sheet of drawing paper. The ability to focus and determine details of color insured identification of the nerve fibers in all parts of the nerve trunk just as though the section were being studied by the usual technic under the microscope. In these respects the method proved far superior to that of counting from photomicrographic enlargements, being more direct, simple and accurate. The magnification obtained by means of the carbon arc projector is comparable to that obtained in photomicrographic enlargements, and the apparatus may be adjusted readily to whatever magnification is most satisfactroy. The accuracy and ease of counting were materially aided by blocking off in pencil on drawing paper each nerve fiber as it was counted. This projection method possesses the advantages of a microscopic study for focusing and for differentiation of color, and the result has the advantages of the enlarged photomicrograph without the faults and difficulties of production of the latter.

RESULTS

The follow-up findings, weights of the muscles and nerve fiber counts for the 4 dogs studied are presented in table 1.

TABLE 1.—*Results of Anastomosis*

	Dog 89	Dog 93	Dog 34	Dog 459
Weight............................	15.3 Kg.	17.0 Kg.	26.0 Kg.	19.5 Kg.
Anastomosis......................	Control— right common peroneal to right common peroneal	Control— right common peroneal ligated; 1 mo. later anastomosed to right sciatic	Right common peroneal to right common peroneal and tibial	Right common peroneal to right common peroneal and tibial
Follow-up studies				
Posture..........................	Normal	Right hock slightly down	Right hock down moderately	Normal
Gait.............................	Normal	Minimal limp	Awkward; often walking on dorsum of right hindpaw	Slight awkwardness
Weakness				
Flexors.........................	None	None	Slight	Slight
Extensors......................	? Slight	Slight	Moderate	Slight
Muscle atrophy				
Flexors.........................	None	None	Moderate	Moderate
Extensors......................	? None	Moderate	Moderate	Moderate
Time and degree of motor recovery	Complete in 7 mo.	80-90% in 9½ mo.	60-70% in 7 mo.	70-80% in 7 mo.
Trophic ulcers....................	None	None	3 sores; no ulcers	None
Hypesthesia......................	? Slight	Slight	Moderate	? Slight
Time and degree of sensory recovery	? Slight hypesthesia for 8½ mo.	Slight hypesthesia persisting for 9½ mo.	Moderate hypesthesia persisting for 7 mo.	? Slight hypesthesia persisting for 7 mo.
Muscle weight and estimated size of muscle fibers (1 = normal) Gastrocnemius muscle				
Right...........................	66.4 Gm.* 1.15	74.2 Gm.* 1.3	70.5 Gm. 1.37	48.5 Gm. 1.3
Left............................	61.8 Gm. 1	72.0 Gm. 1	103.5 Gm. 1	85 Gm. 1
Tibialis anticus muscle				
Right...........................	20.3 Gm. 1.15	15.4 Gm. 1.3	15 Gm. 1.37	15 Gm. 1.3
Left............................	25.8 Gm. 1	26 Gm. 1	31 Gm. 1	32.5 Gm. 1
Nerve fiber counts				
Right sciatic....................	18,016	13,260	23,959	17,820
Right common peroneal (above anastomosis)	5,504	5,026	7,956	7,088
Right common peroneal and tibial (below anastomosis)	7,474 (common peroneal only)	7,557	15,088	12,533
Increase in nerve fibers..........	35.7%	50%	90%	76.8%

* This weight is increased over that of its control. This is of interest in relation to the hypertrophy of the muscle fibers in these muscles but may also represent the limits of error of the method in spite of careful dissection and efforts to control the effects of dehydration.

COMMENT

It is interesting to compare the results obtained in dogs 34 and 499 with those reported by other workers using essentially the same procedure but different technics. The latter are presented in table 2 and are in essential agreement with the results obtained in this study.

Do these results necessarily reflect an increased final innervation and function of muscles? As has been mentioned, the increase in the number of nerve fibers may merely reflect a well known phenomenon concerned with the regeneration of nerves and, as pointed out by Nageotte,[9] may bear no relation to the final reinnervation of muscles.

TABLE 2.—*Comparative Results Obtained by Other Authors with Different Technics*

Author	Kilvington[2]			Milone[8]	Dogliotti[1]		Iovino[12]		
Case	2	3	4	..	1	2	1	2	3
Weight	..	..	..	..	..	..	10.5 Kg.	8 Kg.	9 Kg.
Nerve fiber counts Sciatic	.....	.....	.....	.....	22,350	16,274	15,096	12,472	12,831
Portion of nerve above anastomosis	4,435	7,740	5,826	2,282	7,200	6,790	6,507	4,945	4,530
Portion of nerve below anastomosis	9,982	9,706	8,688	5,131	14,090	10,555	11,075	9,417	9,913
Percentage increase in nerve fibers	125	25.4	49	123	95	55	70	90	118
Weight of muscles Untreated side	.....	.....	.....	.....	72 Gm.	83 Gm.	41.3 Gm.	23.1 Gm.	32 Gm.
Treated side	.....	.....	.....	.....	70 Gm.	81 Gm.	39.5 Gm.	22.75 Gm.	31.5 Gm.
Estimated increase in size of muscle fibers	.....	.....	.....	.....	33%	33%	Larger	Larger	Larger
Degree and time of functional recovery	Incomplete, 3⅔ mo.	Complete, 3½ mo.	Incomplete, 4⅔ mo.		Complete, 7 mo.	Complete, 14 mo.	Complete, 7 mo.	Complete, 8 mo.	Complete, 10 mo.

Evidence has been adduced from two different angles in answer to this question:

1. The results obtained in the control experiment (dog 39) indicate that Nageotte's opinion is justified, at least to a considerable extent. In this instance simple anastomosis of a nerve trunk resulted eight and a half months later in an increase of more than one third in the number of nerve fibers. Yet complete reinnervation of the muscle presumably required only the original number of fibers. The possibility exists that under the conditions of the experiments (i. e., for the reinnervation and regeneration of muscle fibers) more nerve fibers are actually needed and serve a useful physiologic purpose. If this is the case, the same argument holds for the experiments in which Kilvington's procedure was utilized—more nerve fibers are necessary for the same degree of muscu-

lar function. If this is true, an increased number of nerve fibers would not necessarily mean an increased degree of muscular function. Therefore, regardless of the exact interpretation, the results suggest that the phenomenon of luxuriant regeneration of nerves does not bear a direct quantitative relation to reinnervation of muscles and final return of muscular function.

2. A study of the muscles reinnervated after the Kilvington procedure reveals further evidence bearing on this same question. As may be seen from tables 1 and 2, the weight of muscles on the side operated on was appreciably lower in both instances (dogs 34 and 499) than on the opposite side, used as a control. Likewise, it is to be noted that the muscle fibers on the side operated on were uniformly larger than those on the side not operated on. Volume for volume, therefore, the

TABLE 3.—*Estimated Number of Muscle Fibers Successfully Reinnervated*

	Dog 34		Dog 499	
	Gastroc-nemius	Tibialis Anticus	Gastroc-nemius	Tibialis Anticus
Weight of muscles Untreated side......................	103.5 Gm.	31 Gm.	85 Gm.	32.5 Gm.
Treated side.........................	70.5 Gm.	15 Gm.	48.5 Gm.	15 Gm.
Estimated size of muscle fibers (normal = 1) Untreated side.....................	1	1	1	1
Treated side.........................	1.37	1.37	1.3	1.3
Estimated percentage of fibers in muscles on treated side (percentage of fibers on untreated side = 100)......	50	35	44	35

fibers on the side operated on must be fewer. This fact, combined with the over-all diminution in size of the muscle on the side operated on, as measured by the respective weight of each, yields interesting estimates (table 3), on a percentage basis, of the number of fibers in muscles on the side operated on as compared with their respective controls (100 per cent) on the normal side.

By the Kilvington procedure as used in this study, however, the common peroneal nerve alone supplied the nerve fibers for both extensor and flexor muscles. The number of fibers in this nerve is roughly 30 per cent or more of the number present in the sciatic nerve. Also, the estimated number of regenerating muscle fibers in the extensor muscles on the side operated on, as judged from the tibialis anticus muscle, is 35 per cent, while the flexor muscles on the side operated on are estimated to have approximately 44 to 50 per cent of their normal number of muscle fibers.

Since the flexor muscles are more than twice the size of the extensor muscles it may be safely estimated that the number of successfully reinnervated muscle fibers after the Kilvington procedure as performed in

this study is at least 10 per cent greater than the original number of extensor muscle fibers normally innervated by the common peroneal nerve. This is shown diagrammatically in the accompanying illustration.

This evidence tends to support Dogliotti's contention. It is to be noted, however, that in these two experiments the increase in the numbers of regenerating nerve fibers was 76.8 and 80 per cent. These figures are markedly out of proportion to the number of muscle fibers estimated to have been successfully reinnervated. Also, since the follow-up observations (table 1) are in harmony with the findings for the muscles, it may be concluded that regeneration of the nerves was also out of proportion to the return of muscular function.

Even though reinnervation and return of function of the muscles are not in proportion to the regeneration of the nerves after the Kilving-
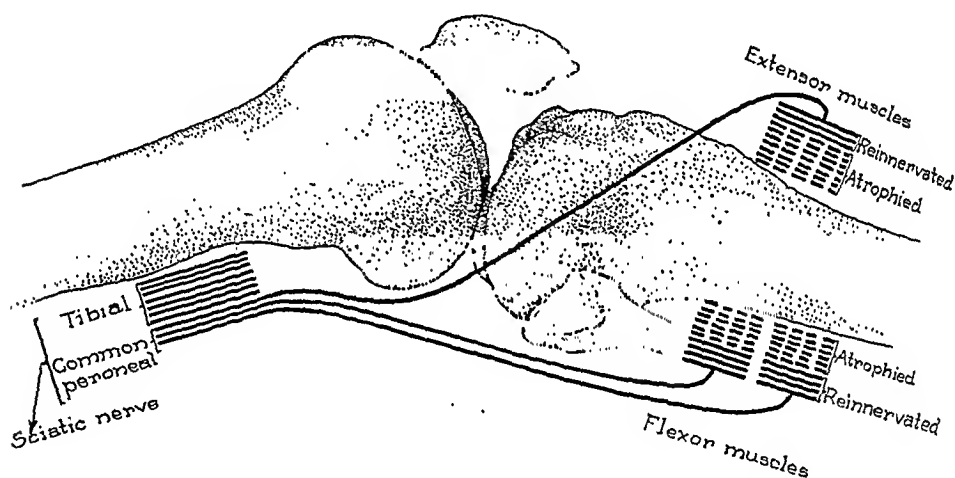
Diagram illustrating the estimated reinnervation of muscles after anastomosis of the proximal end of the common peroneal nerve to the peripheral ends of the tibial and the common peroneal nerve combined. The sciatic nerve fibers are represented by ten lines; the extensor muscle fibers are represented by ten lines, and the flexor muscle fibers are proportionately represented by twenty lines. The broken lines indicate (relatively) the estimated number of muscle fibers not successfully reinnervated. It should be noted that the total number of unbroken "muscle lines" is eleven, while the relative number of "extensor muscle lines," representing muscle fibers normally innervated by the common peroneal nerve, is ten.

ton procedure, the important fact remains that it may be possible by this method to obtain reinnervation and functional recovery of the paretic muscles when the paresis is on a peripheral neurogenic basis.

If a partially paralyzed nerve is severed and immediately anastomosed, an increase of muscular reinnervation and function may reasonably be expected. If a neighboring intact nerve is selected for the anastomosis in the case of a completely or almost completely paralyzed

nerve, there results a diminution in the strength and function of the muscles normally innervated by the intact nerve, considerable recovery in the muscles innervated by the paralyzed nerve and an over-all increase in the number of muscle fibers innervated by the intact nerve. Although the return of strength and function may not be so great as Dogliotti estimated, it is still possible that the procedure may be of practical advantage in properly selected cases. The good results obtained in the control experiment (dog 93) tend to support this idea. In this instance an attempt was made to simulate the condition mentioned by ligating the common peroneal nerve and producing paralysis of the extensor muscles of the right hindleg. One month later the Kilvington procedure was carried out in the same manner as for dogs 34 and 499. In spite of the previous damage to nerves and muscles and an increase of only 50 per cent in the regeneration of the nerves anastomosed to the common peroneal nerve, good reinnervation of the muscle and return of · function occurred.

The possibility of good functional reinnervation of two synergistic groups of muscles by the nerve supplying one of these muscle groups, as demonstrated by Kilvington,[2] by Kennedy[3] and by this study, is also of great significance from the standpoint of the practicability of this procedure. If an extensor muscle of the foot, for example, were paralyzed, a fair functional result might reasonably be expected to follow section of one of the branches from the tibial nerve to the gastrocnemius or the soleus muscle and its anastomosis to the distal ends of both the same branch and the common peroneal nerve. Although such an instance might offer a promising opportunity for employment of the Kilvington procedure, it is possible that other conditions might not be so favorable. In the proper selection of cases the following limiting factors should be mentioned:

(*a*) If an intact nerve is selected for the anastomosis the procedure will result in permanent weakening of the muscles previously and normally supplied by that nerve. Hence, only nerves or branches of nerves the loss or partial loss of which will not cause appreciable weakness or loss of function should be selected. Without proper care in this respect the procedure may conceivably result in as much paralysis as that which it is proposed to cure, or more. Indeed, the use of an intact nerve for this procedure does not yet appear to be justified. Because the estimation of functional recovery is so difficult with animals and conclusions based on experimental work frequently require modification when applied to human conditions, any recommendation in this regard (i. e., the use of intact nerves) must be deferred until further data are available on the degree of functional recovery following this procedure (i. e., the use of a partially paralyzed nerve) in man.

(*b*) Reinnervation and recovery of the extensor muscles of the leg are considerably poorer than reinnervation and recovery of the flexor muscles, as shown by the work of Kilvington,[2] that of Dogliotti[1] and the present study. In our experience this was true even though the nerve to the extensor muscles (common peroneal) was selected for the anastomosis (table 1). Thus, in this procedure, the use of the intact common peroneal nerve or its branches should be avoided as far as possible.

(*c*) As has been determined by another experimental study now in progress, an important limiting factor in functional recovery is probably fibrosis of the muscle fibers. Since muscular fibrosis progresses with continued paresis, intervention should take place reasonably early.

CONCLUSIONS

1. Sectioning of the sciatic nerve and immediate anastomosis of the proximal portion of the common peroneal to the peripheral ends of both the common peroneal and the tibial nerve resulted under experimental conditions in a marked increase in the number of regenerating nerve fibers below the point of anastomosis.

2. Reinnervation of muscles and recovery of function following this procedure were increased over the innervation and function originally mediated by the common peroneal nerve alone but under the conditions of this study were not proportional to the luxuriant regeneration of the nerve.

3. Synergistic groups of muscles may be reinnervated successfully and good functional recovery obtained by anastomosis of a nerve supplying one of these muscles to the peripheral portions of the nerves innervating both the groups of synergistic muscles. The flexor muscles of the leg showed recovery considerably better than that of the extensor muscles, even though the common peroneal nerve was selected for the anastomosis.

4. In properly selected cases the sectioning and immediate anastomosis of a partially paralyzed nerve (as, for example, the common peroneal nerve with marked paresis involving the tibialis anticus and the extensor digitorum longus muscle) may prove of practical advantage for treating the isolated paresis occurring in association with poliomyelitis and other peripheral neurogenic paralyses.

FIBROCYSTIC DISEASE OF THE BREAST

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The diversity of terms applied to proliferative and cystic changes in the breast since the recognition of such changes over a century ago illustrates the efforts made to interpret the varied clinical, pathologic and anatomic findings.

The condition was first described by Cooper [1] in 1829, in the chapters on "hydatid," "irritable" and "chronic" mammary tumor in his "Illustrations of the Diseases of the Breast." Included in the early nomenclature are such terms as "abnormal involution of the breast," [2] "cystic disease of the breast (Reclus' disease)," [3] "sero-cystic tumors of the breast," [4] "chronic cystic mastitis," [5] "chronic cystic mastopathia," [6] "cystadenoma (Schimmelbusch's disease)" [7] and "senile parenchymatous hypertrophy." [8a] Later, Bloodgood wrote of "shotty breast" and "blue-domed cyst." [8b] Cheatle and Cutler [9] added "mazoplasia" and "cystiphorous desquamative hyperplasia"—conditions of the breast which, they concluded, differ biologically and morphologically from one another and which together represent the condition generally included in the

1. Cooper, A.: Illustrations of the Diseases of the Breast, London, Longman, Rees & Co., 1829, pt. 1.

2. Warren, J. C.: Surgical Observations on Tumors, with Cases and Operations, Boston, Crocker & Brewster, 1837.

3. Reclus, P.: La maladie kystique des mamelles, Bull. Soc. anat. de Paris 58:428, 1883.

4. Brodie, B. C.: Clinical Lectures in Surgery, Philadelphia, Lea & Blanchard, 1846, p. 206.

5. König, F.: Mastitis chronica cystica (interstitielle Mastitis, Cystadenoma mammae, Maladie de Reclus), Centralbl. f. Chir. 20:49 (Jan. 21) 1893.

6. Aschoff, L.: E giustificata l'ammissione di uno stadio preblastomatoso e precanceroso? Tumori 10:337 (July-Oct.) 1936.

7. Schimmelbusch, C.: Das Cystadenom der Mammae, Arch. f. klin. Chir. 44:117, 1892.

8. Bloodgood, J. C.: (a) Senile Parenchymatous Hypertrophy of the Female Breast: Its Relation to Cyst Formation and Carcinoma, Surg., Gynec. & Obst. 3:721 (Dec.) 1906; (b) Pathology of Chronic Cystic Mastitis of the Female Breast, with Special Consideration of the Blue-Domed Cyst, Arch. Surg. 3:445 (Nov.) 1921.

9. Cheatle, G. L., and Cutler, M.: Tumors of the Breast, London, Edward Arnold & Co., 1931.

one term "chronic mastitis" or "chronic cystic mastitis." Others [10] subsequently suggested "cystoplasia" as an abbreviation of "cystiphorous desquamative hyperplasia." The condition has also been designated "fibrocystic mastitis" at the New York Post-Graduate Medical School and Hospital.[11] Lewis and Geschickter,[12] on the other hand, used the term "chronic cystic mastitis" to cover the entire condition but recognized two different types, to which they applied the names "cystic disease of the breast" and "adenosis of the breast." "Mastopathia" was regarded by Whitehouse [13] as an appropriate term for the entire picture, in which he included mammary pain and swelling, oligomenorrhea and menstrual headache. Taylor [14] suggested "adenofibrosis," which, he stated, is in harmony with the nomenclature employed for pathologic conditions of the reproductive tract and is similar to the term "fibroadenomatosis cystica mammae," which was adopted by Semb [15] after exhaustive histologic studies.

While it is realized that the condition under discussion is already overburdened with diversified names, it is in the hope of diminishing rather than of adding to the confusion that another title is herewith suggested. The term "fibrocystic disease of the breast" has been chosen because it seems definitely to characterize the outstanding features of the condition, namely, the fibrous and cystic elements. The classification on which this is based is similar to that of Lewis and Geschickter.[12a] The classification here presented, however, recognizes three types of the disease instead of only two. They are: (1) the predominantly cystic type (which includes "Schimmelbusch's disease" and "blue-domed cyst") ; (2) the type in which the fibrous element predominates ("adenomatosis," or "shotty breast"), and (3) the type in which both fibrous and cystic elements are present in approximately equal proportions.

10. Ritvo, M.; Butler, P. F., and O'Neil, E. E.: Roentgen Diagnosis of Tumors of the Breast, J. A. M. A. **105**:343 (Aug. 3) 1935.

11. Russell, T. H.: Personal communication to the author.

12. Lewis, D., and Geschickter, C.: (*a*) Ovarian Hormones in Relation to Chronic Cystic Mastitis, Am. J. Surg. **24**:280 (May) 1934; (*b*) Endocrine Therapy in Chronic Cystic Mastitis, J. A. M. A. **109**:1894 (Dec. 4) 1937.

13. Whitehouse, B.: Mastopathia and Chronic Mastitis, Surg., Gynec. & Obst. **58**:278 (Feb. 15) 1934.

14. Taylor, H. C., Jr.: Relation of Chronic Mastitis to Certain Hormones of the Ovary and Pituitary and to Coincident Gynecological Lesions: I. Theoretical Considerations and Histological Studies, Surg., Gynec. & Obst. **62**:129 (Feb. 1) 1936.

15. Semb, C.: Fibroadenomatosis Cystica Mammae, Acta path. et microbiol. Scandinav. (supp.) **5**:62, 1928.

PHYSIOLOGIC CONSIDERATIONS

The development of the breast with its activities has been conveniently divided by Turner [16] into six stages: (1) the embryonic and fetal period, (2) the interval between birth and puberty, (3) the period of recurring estrus cycles, (4) pregnancy, (5) lactation and (6) involution. Development of the mammary gland during the first two stages is the same in both sexes. With the approach of puberty and maturation of the ovaries, definite changes occur in the female breast; there is further growth of the duct system and of the connective tissue stroma. These changes, coincident with others elsewhere in the body, indicate the role of the mammary gland in the reproductive system. Disturbance in any of the reproductive organs invariably alters the development and function of the mammary glands. This was understood by Sir Astley Cooper [1] in 1829, when he hypothesized a causal correlation of disease of the uterus and other organs with certain morbid processes in the breast. In 1846 Brodie [4] called attention to the restriction of "sero-cystic tumors of the breast" to the period of sexual activity. These outstanding observations served as stimuli for further investigation.

Much interest has centered on the physiologic processes concerned with the menstrual cycle. Rosenburg [17] was the first to correlate histologic changes in the breast with changes in the ovaries. Others [18] also noted characteristic variations in the epithelium and in the connective tissue of the breast during the premenstrual, the menstrual and the resting stage of the monthly cycle. It has been observed that changes in the breast during menstruation are like those occurring during pregnancy but that they are present to a lesser degree. The glands increase in number, and there is hyperplasia of the epithelium and connective tissue stroma. If there is no conception, the gland returns to normal within two or three days after menstruation. Conception, however, with its concomitant physical changes, stimulates the breast to complete its development for ultimate function.

Until the close of the last century the nervous system alone was believed to be the factor coordinating the activities of the mammary glands with those of the ovaries, uterus and placenta. Studies on pregnant and nursing animals—through the isolation of the mammary

16. Turner, C. W.: Mammary Glands, in Allen, E.: Sex and Internal Secretions, Baltimore, Williams & Wilkins Company, 1932, pp. 544 and 583.

17. Rosenburg, A.: Ueber menstruelle, durch das Corpus luteum bedingte Mammaveränderungen, Frankfurt. Ztschr. f. Path. **27**:466, 1922.

18. (*a*) Dieckmann, H.: Ueber die Brustdrüse bei gestörtem und ungestörtem Menstruations-Ablauf, Virchows Arch. f. path. Anat. **256**:321, 1925. (*b*) Moskowicz, L.: Ueber den monatlichen Zyklus der Brustdrüse, Arch. f. klin. Chir. **142**:374, 1926. (*c*) Litten, L.: Die histologischen Grundlagen der Sekretion nichtgravider Mammae, Virchows Arch. f. path. Anat. **259**:126, 1926.

gland from all nervous connections—seemed to prove the fallacy of this theory. Other avenues of investigation have since been followed, leading gradually to present theories of endocrine activity in the development of the breast not only during the prepubertal and pubertal periods, pregnancy and lactation, but during the climacteric as well. The ovarian hormones taking part in the initiation and in the final stages of the cycle are still subjects of debate among investigators.

ENDOCRINE INTERRELATION

The accompanying chart indicates hormonal influences, both known and suspected, affecting the breast. It is a composite drawing from various sources.[19]

Special interest has centered about the role of the anterior lobe of the pituitary gland in the endocrine cycle. Although much is still problematic, it is generally assumed that its influence is exerted through two of its gonadotropic substances, *A* and *B*, known respectively as the follicle-stimulating hormone and the luteinizing hormone. The *A* component activates the growth of the graafian follicle and its granulosal cells, to elaborate estrogen, a substance which experimentally produces estrus in rodents. Estrogen, in turn, in addition to producing edema and hyperemia, stimulates proliferation of the basal layer of the uterine endometrium (follicular phase, or follicular-endometrial stage). The *B* component, the luteinizing factor, stimulates the ruptured graafian follicle to formation of corpora lutea. Progestin, the active principle of the corpus luteum, is responsible for the secretory alteration of the previously estrogen-stimulated endometrium, which results in the characteristic premenstrual phase of the cycle (luteal phase, or luteal-endometrial stage).

Evidence of the lack of progestin is best shown by the fact that without follicular rupture the endometrium of the follicular (preovulation) phase does not advance to the luteal (secretory) phase, because if

19. (*a*) Estrogenic Substances: Theelin, report of the Council on Pharmacy and Chemistry, J. A. M. A. **100**:1331 (April 29) 1933. (*b*) Heyd, C. G.: Hyperthyroidism, S. Clin. North America **5**:379 (April) 1925. (*c*) Frank, R. T., and Unger, A.: An Experimental Study of the Causes Which Produce the Growth of the Mammary Gland, Arch. Int. Med. **7**:812 (June) 1911. (*d*) Novak, E.: The Treatment of Primary Dysmenorrhea with Especial Reference to Organotherapy, Am. J. M. Sc. **185**:237 (Feb.) 1933. (*e*) Doisy, E. A.; Veler, C. D., and Thayer, S.: The Preparation of the Crystalline Ovarian Hormone from the Urine of Pregnant Women, J. Biol. Chem. **86**:499 (April) 1930. (*f*) Neustaedter, T.: Modification of Frank-Goldberger Blood Estrin Test, Endocrinology **20**:639 (Sept.) 1936. (*g*) Frank, R. T.: The Role of the Female Sex Hormone, J. A. M. A. **97**:1852 (Dec. 19) 1931. (*h*) Aschheim, S., and Zondek, B.: Hypophysenvorderlappenhormon und Ovarialhormon im Harn von Schwangeren, Klin. Wchnschr. **6**:1322 (July 9) 1927.

the follicle fails to rupture no corpus luteum is formed to supply the progestin. An atretic follicle results.

Based on the presence of definite amounts of estrogen in the blood and urine of normal fertile women, deviations from the normal may be determined during the menstrual cycle and climacteric period [19f, g] and during pregnancy.[20] When the concentration of estrogen in the blood reaches a peak, it inhibits the *B* component of the anterior lobe of the
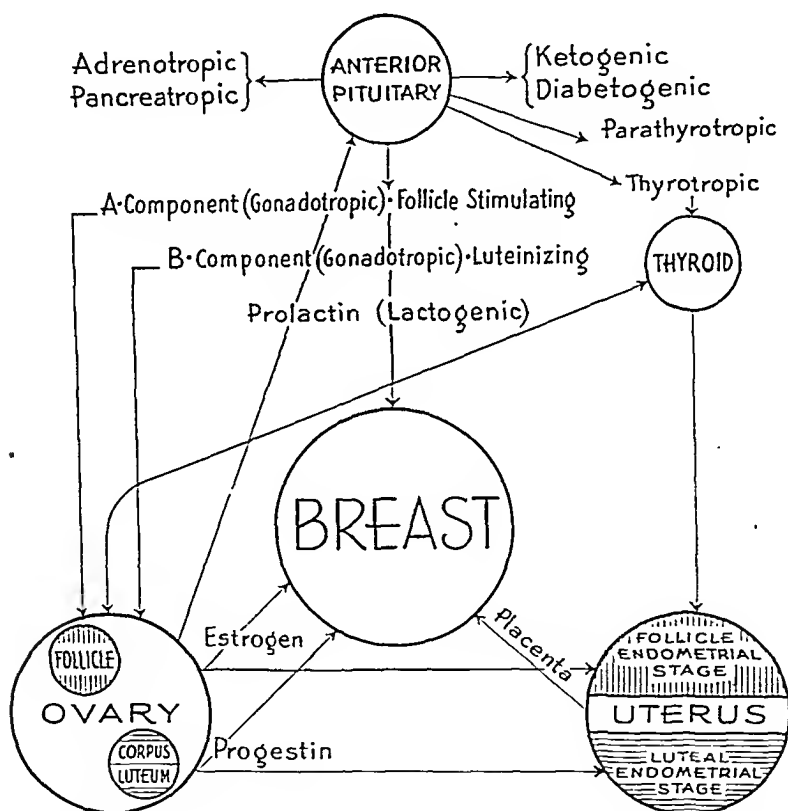
Schematic diagram of the interrelations of the hormones affecting the breast.

pituitary gland. As a result, the corpus luteum degenerates and gradually ceases to function, finally becoming the corpus albicans. This occurs after ovulation with nonfertilization of the ovum and coincides with the onset of menstruation. Hence, the abrupt withdrawal of estrogenic substance is interpreted by some to be the initiating factor of menstrua-

20. Frank, R. T.; Goldberger, M. A., and Spielman, F.: A Method for Demonstrating the Prepituitary Maturity Hormone in the Blood of Non-Pregnant Women, Proc. Soc. Exper. Biol. & Med. 28:999 (June) 1931.

tion, being manifested by the leukocytic invasion and collapse of the endometrial glands, desquamation and hemorrhage due to destruction of the capillary bed and to bleeding caused by rhexis. The premenstrual mammary syndrome usually also subsides at this time.

With fertilization of the ovum, however, the corpus luteum (corpus luteum of pregnancy) persists, and production of estrogen and progestin continues, the estrogen constantly increasing up to full term, whereas the progestin decreases after the sixth month. Mammary changes continue to the stage of lactation, after the decidua capsularis of the nidatory endometrium and the trophoblastic cells of the fertilized ovum become the placenta. Gonadotropic substance is recoverable from the urine during the period of gestation. The Aschheim-Zondek test [19h] is based on the presence of this substance in the urine.

The lactogenic substance (prolactin) of the anterior lobe of the pituitary has been identified and assayed.[21] It produces mammary hypertrophy such as is associated with pregnancy and lactation, but only in breasts previously subjected to the influence of estrogen.

It is not unlikely that aberrations in the reciprocal relation or disturbances in the equilibrium ratio of the various hormones may produce abnormal involution of the breast, giving rise to fibrocystic disease and its associated disturbances. Aschoff[6] characterized the disease as "preblastomatous [preneoplastic], dishormonal type," indicating the cause. Similar views were expressed by Franzas[22] when he wrote:

> The epithelial proliferation is probably activated by an abnormally altered sex hormone. For this to take place, a part, at least, of the gland parenchyma must be well enough preserved so that the pathological stimulus can reach the pathological threshold of epithelial proliferation.

CLINICAL MANIFESTATIONS

Fulness and enlargement of the breast are among the symptoms of fibrocystic disease, often associated with sensations of tingling to the point of actual pain, and recurring with notable regularity prior to or at the onset of menstruation. The pain in the breast is generally intermittent, and excessive tenderness may be present. In about 20 per cent of cases[23] pain radiates to the chest, shoulder or arm. Bleeding or

21. Riddle, O.; Bates, R. W., and Dykshorn, S. W.: The Preparation, Identification and Assay of Prolactin—A Hormone of the Anterior Pituitary, Am. J. Physiol. **105**:191 (July) 1933.

22. Franzas, F.: Ueber die Mastopathia cystica latenta und andere bemerkenswerte Veränderungen in klinisch symptomfreien weiblichen Brüsten, Arb. a. d. path. Inst. d. Univ. Helsingfors **9**:401, 1936.

23. Taylor, H. C., Jr.: Gynecological Aspects of the Etiology and Treatment of Chronic Mastitis, Surg., Gynec. & Obst. **57**:627 (Nov.) 1933.

discharge from the nipple may accompany these symptoms. The condition is usually bilateral; in older persons, however, it may be confined to one breast.

Fibrocystic disease may be without symptoms, as the work of Franzas [22] indicates. He investigated 200 breasts from 100 cadavers of women 18 to 90 years of age. All the women had been in a hospital for a longer or shorter time before death. None of the clinical symptoms of mammary disturbance had been present. In cases in which the history was defective, relatives of the deceased were questioned. Each breast, with areola and nipple, was divided into quadrants, and two sections were taken from each quadrant. When results were negative, Franzas took further sections from such breasts. For comparison, microscopic sections of the breasts of several dozen patients with fibrocystic disease (proved clinically) were used, as well as a number of various mammary tumors.

In 55 per cent of the 100 cases in which no symptoms had been present there were cyst formations similar to those of fibrocystic disease; in 25 per cent the condition was bilateral. In such cases of clinically latent disease, the connective tissue was not more prolific than in breasts not showing the cystic changes. Franzas failed to mention a comparison with connective tissue changes in clinically demonstrable fibrocystic disease. Schultz,[24] for example, wrote definitely of "the never-failing connective tissue increase . . . of the cystic breast." This increase in connective tissue, as compared with the absence of such increase in the latent form, may perhaps be linked to the fibrocystic disease becoming clinically manifest. Aschoff [6] also stated that this disease "may be called epitheliofibrous because it is representative of the irregular new growth of the glandular epithelium and of the connective tissues . . . ."

On palpation, the breasts may be practically normal in consistency or diffusely nodular, as in so-called "shotty breast." More often, however, there are moderately firm, irregular, freely movable masses, varying in size from 1 to 10 cm. Taylor [23] observed the appearance, intermittently, of a premenstrual lump in about 7 per cent of a series of 102 cases and a constant lump in about 11 per cent.

The age incidence varies, as observed by different authors. In the majority of 600 cases reported by Lewis and Geschickter [12a] the condition occurred in women between the ages of 35 and 45 years; in another series [13] of painful nodular breasts, the average age was 35 years. In approximately 80 per cent of Taylor's [23] series the patients were between 20 and 40 years; in 15 per cent, between 40 and 50 years, and

24. Schultz, A.: Die Zystenmamma, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1933, vol. 7, pt. 2.

in 5 per cent, between 15 and 20 years. Fibrocystic disease of the breast is seen more frequently at an earlier age in nulliparae than in women who have undergone pregnancy and lactation. Although far less frequent than in the female, fibrocystic disease of the breast does occur in the male; 9 cases have been reported in which the condition occurred in male patients aged 14 to 48 years.[25]

PATHOLOGIC AND ANATOMIC PICTURE

There is a great difference of opinion as to the interpretation of the pathologic and anatomic character of the disease. Cheatle and Cutler [9] regarded the entire condition as one of "desquamative epithelial hyperplasia" which, they concluded, embraces two distinct states, differing widely both biologically and morphologically. These they called "mazoplasia" and "cystiphorous desquamative epithelial hyperplasia." Mazoplasia is defined as a process closely related to that of normal involution—a physiologic aberration which returns to normal at the menopause. The same condition may be found in the breast at birth and during pregnancy and lactation. There is desquamation of the epithelial cells of the terminal ducts and acini, accompanied by hyperplasia of the pericanalicular and periacinous connective tissue. Pain is attributed to distention of the acini and ducts, which are occluded by the accumulation of desquamated epithelial cells. In mazoplasia, the hyperplasia remains stable, forming neither cysts nor papillomas, being thereby distinguished from "cystiphorous desquamative epithelial hyperplasia" which Cheatle and Cutler identified as the condition usually referred to by others as "chronic cystic mastitis," Reclus' disease or Schimmelbusch's disease. In this cystic condition epithelial neoplasia may gradually develop—a process which likewise is never associated with mazoplasia. Cheatle and Cutler concluded that fibroadenoma, which occasionally forms, is the only lesion which may be ascribed to mazoplasia.

Whitehouse [13] was among those who disagreed with Cheatle and Cutler. In a pathologic and anatomic study of a large series of cases in which the condition was classified as "chronic mastitis," he reported the following findings and conclusions: 1. The condition described as "mazoplasia" is commonly associated in the same organ with the lesion described as "cystiphorous hyperplasia." 2. In both lesions epithelial hyperplasia is the preliminary dominant factor, and in both large numbers of pathologic lymphocytes are constantly present. 3. "Mazoplasia" in the adult appears to be the natural result of excessive stimulation of the mammary epithelium by the luteal hormone. 4. This

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25. Campbell, O. J.: Relationship Between Cystic Disease of the Breast and Carcinoma, Arch. Surg. **28**:1001 (June) 1934.

excessive stimulation results in production of excessive secretion followed by cystic disease, the formation of cysts apparently representing a breakdown in the normal balance between production and absorption. The fluid from these cysts was found to contain colostrum cells and epithelium in the process of autolysis, but no fibrin. No coagulation occurred. Fat was found in some specimens, while others contained urea and uric acid. Because he regarded "mazoplasia" as a disorder of function, Whitehouse concluded that it is pathologic and not physiologic, even if it is a frequent condition.

Lewis and Geschickter [12a] studied human material obtained at definite periods during the menstrual cycle and pregnancy, as well as tissue from experimental animals after injection of estrone (theelin) and progestin. They concluded that "chronic cystic mastitis"—which they classified as (1) cystic disease of the breast and (2) as adenosis of the breast—corresponds to alterations in the character, amount or periodic discharge of the ovarian hormones, estrogen and progestin. An analysis of 600 cases of this condition is reported in support of their theory.

As has been stated, the pathologic-anatomic picture of the disease, as viewed by me, embraces three distinct types instead of the two outlined by Lewis and Geschickter.[12b]

In the cystic type of the condition there are dirty gray, firm, slightly elastic areas, not always well limited. A variable number of cysts are present, the individual cyst varying in size from that of a split pea to that of a walnut. Because of the translucency of the cyst wall, many unruptured cysts appear blue—"blue-domed" cyst, so named by Bloodgood.[6b] The content of the cyst varies; it may be clear and fluid or thick and creamy. It is never bloody as in a papillomatous cyst. The ducts are at times greatly dilated with material resembling Camembert cheese, composed largely of cast-off epithelium.

The most common microscopic picture (perhaps representing an early stage of the disease) is that of a double outline to the cells lining the glands or ducts. Another picture includes a lining of closely packed, multilayered polyhedral epithelial cells. These may form papillomatous projections into gland or duct spaces and may even unite with those of the opposite side to form bridges. The proliferating epithelial cells may completely fill the lumen. Not infrequently, so-called pale epithelium may be seen; in this the cells are cuboidal, staining pink with eosin (normally the cell body is more neutrophilic). The cytoplasm has the appearance of being composed of fine droplets. The pale character and shape of the cells strongly suggest sweat gland epithelium.

The histologic appearance may vary in different portions of the same specimen, and to obtain a complete picture it is essential to examine several sections. There may be epithelial hyperplasia, dilatation of the

lactiferous ducts (cyst of Brodie) or increase in stroma as well as infiltrative cells, which are usually seen in the presence of inflammation. Although Schimmelbusch [7] concluded that there is an increase of the acini in single lobules, his view has not been generally accepted.[24]

The increase of connective tissue stroma in some areas may suggest fibroadenoma; Schultz [24] spoke of adenomatous nodules, or microadenoma, as well as of cystadenoma, papillary and intracanalicular, both single and multiple. In young persons this increase lends a characteristic firmness to the breast; the connective tissue is denser and more hyalinized than in the senile breast. When compared with the epithelial elements—glands and ducts which are lined by low columnar to cuboidal as well as by flattened epithelium—the connective tissue in certain areas may predominate. Cast-off cells and even cholesterol crystals from the lipoid elements of the epithelial cells may be found in the cystic spaces; at times foreign body giant cells may be seen about the crystals.

The relation of fibrocystic disease of the breast to carcinoma is still actively debated, notwithstanding the numerous investigations devoted to the problem. While some authors [26] have concluded that fibrocystic disease cannot be regarded as a forerunner of carcinoma, Aschoff [6] wrote that "On the soil of such dishormonal preblastomatous proliferations [fibrocystic disease], there can easily be implanted the true blastomatous formation, benign or malignant."

According to Cheatle and Cutler,[9] approximately 20 per cent of all carcinomas of the breast start within the lesion of the "cystiphorous desquamative epithelial hyperplasia." A cyst may be present during the end of the second and in the early years of the third decade of life; during the next decade it may gradually pass into a state of benign epithelial neoplasia; the same lesion may then develop into a carcinoma (usually during the late forties or early fifties).

Rodman [27] found carcinoma associated with "chronic cystic mastitis" in 15.5 per cent of 100 patients of various ages. Whether or not malignant tumor develops from the preexisting cystic disease is a question which he believes must wait on discovery of the actual cause of cancer.

Bloodgood [8a] in 1906 regarded "chronic cystic mastitis" as a precancerous state. In 1921, after years of study and follow-up of typical cases, he completely reversed his opinion.[8b] He concluded [28] that cancer

26. Lewis and Geschickter.[12b] Franzas.[22]

27. Rodman, J. S.: Chronic Cystic Mastitis: A Further Report on the Nature of the Process, Am. J. Surg. 28:452 (May) 1935.

28. Bloodgood, J. C., in discussion on Geschickter, C.: The Early Literature on Chronic Cystic Mastitis, Bull. Johns Hopkins Hosp. 55:256 (June) 1934.

is a much less frequent occurrence in a breast with this disease than in the normal, the pregnant or the lactating breast. Campbell,[25] on the basis of a follow-up system of from three to ten years in over 200 cases in which the condition was treated either by local excision or by simple amputation, arrived at the same conclusion. Trout [29] and Harvey,[30] among others, agreed with this opinion, the latter believing that the disease "is an entity in itself, and should be so considered." In one series [12b] of 1,048 cases, 523 were followed for five years. Of this number carcinoma developed in less than 1 per cent (4 patients).

The solution of this problem is difficult, not only because both fibrocystic disease and malignant tumor generally affect persons of middle age or persons still older, but also because the etiologic factors of both conditions are still undetermined.

CAUSES

Lack of natural drainage of the products of secretion in the breast, which otherwise find an outlet when the mouths of the mammary glands open more widely during lactation, was pointed out by Keynes [31] as a possible etiologic basis of "chronic mastitis." The significance of this observation lies in the fact that the disease occurs less often in normally lactating mothers than in those who have suffered interrupted pregnancies or miscarriages or in unmarried women. The chemical nature of the stagnating secretion and epithelial débris and the frequent presence of associated carcinoma in the same breast suggested that both conditions might be due to the same factor. The findings of Adair [32] seem to lend emphasis to the theory of Keynes. Analysis of cellular débris in a series of 200 cases of mammary cancer showed that it contained both lactic and butyric acid. According to Adair, "these are considered to be an important part of those irritating factors responsible for the tissue reactions resulting in hypertrophy, precancerous changes and eventually cancer." It is pertinent that, as among women with fibrocystic disease, only a small proportion (8.5 per cent) had a history of normal lactation or of lactation entirely free from accidental incidents leading to impaired drainage. His findings were corroborated experi-

29. Trout, H. H.: Carcinoma of the Breast: A Study in Etiology and Prognosis, Am. J. Surg. 24:258 (May) 1934.

30. Harvey, S. C.: Chronic Cystic Mastitis as a Physiological Aberration and Its Significance in the Diagnosis and Treatment of Tumors of the Breast, Yale J. Biol. & Med. 7:521 (July) 1935.

31. Keynes, G.: Chronic Mastitis, Brit. J. Surg. 11:89 (July) 1923.

32. Adair, F. E.: Etiological Factors of Mammary Cancer in Two Hundred Women; Also a Control Study of One Hundred Normal American Women, New York State J. Med. 34:61 (Jan. 15) 1934.

mentally; cancer of the breast was produced in 87 per cent of a group of mice by means of artificial stagnation.[33]

Fibrocystic disease of the breast is often coincidental with pathologic conditions of the pelvis, including inflammatory lesions, cysts, fibroids, displacements or prolapse; a beneficial effect on mammary symptoms or their complete elimination occurs in many cases with successful treatment of the pelvic condition. The process by which this relation is established is still open to question. Of importance is the fact that in many cases fibrocystic disease occurs in women of nervous or hysterical temperament and that exacerbations sometimes follow a shock or great excitement. In this connection one cannot fail to observe a rather general tendency at present to revert to the theory involving the nervous system in the activities of the mammary gland—a theory previously referred to and one which had apparently been disproved at the end of the last century. Recent discussions have been concerned with the process of lactation and its bearing on pathologic conditions of the breast. Nelson[34] in a résumé of recent contributions to the subject concluded that development of the breasts and initiation of the secretion of milk are apparently under purely endocrine control, but that a nervous mechanism (in the reflex stimulation of the hypophysis) is probably instrumental in the maintenance of lactation. Clinically it has been demonstrated that lactation occurs in response to hormonal stimulation by intramuscular injection of pituitary lactogenic substance (prolactin).[35]

The frequent aggravation of mammary symptoms at the onset of menstruation seems to point to an endocrine factor. Fibrocystic disease of the breast is observed frequently in women who menstruate at frequent intervals; this suggests a disturbance in the production of estrogen or in that of progestin. Such women are low in potency, because the cyclic bleeding is usually anovulatory. Under such circumstances the ovum does not leave the follicle, and a corpus luteum does not form to stimulate the development of a good pregravid (luteal) endometrium. Irregular menstruation and interrupted pregnancies are often associated with fibrocystic disease of the breast. A review of the literature leaves little doubt that such mammary changes

33. (*a*) Bagg, H. J.: The Role of Functional Activity in the Production of Mammary Carcinoma, Am. Naturalist **60**:234, 1926. (*b*) Adair, F. E., and Bagg, H. J.: Breast Stasis as the Cause of Mammary Cancer, Internat. Clin. **4**:19 (Dec.) 1925.

34. Nelson, W. D.: Endocrine Control of the Mammary Gland, Physiol. Rev. **16**:488 (July) 1936.

35. Kurzrok, R.; Bates, R. W.; Riddle, O., and Miller, E. G., Jr.: The Clinical Use of Prolactin, Endocrinology **18**:18 (Jan.-Feb.) 1934.

are the result of repeated and perhaps aberrant stimulation by progestin and by the associated substances estrogen and the pituitary lactogenic factor (prolactin).

Methods of determining the amount· of estrogenic substance in the blood and urine [36] have greatly facilitated the diagnosis of underlying glandular disturbances. The tests are comparable to tests for determining the basal metabolic rate in functional disorders of the thyroid or to studies of calcium and phosphorus in disturbance of the parathyroid glands.

Transillumination and roentgen examination are additional methods of considerable value in the diagnosis of fibrocystic disease. With transillumination many of the larger "blue-domed" cysts and other mammary conditions of altered density are more readily recognized. In distinguishing a hematoma from a solid tumor transillumination is of great advantage.

Roentgenographic study is also helpful in determining the presence of a neoplasm.[10] In viewing the breast roentgenologically it is important to remember that the various phases of the menstrual cycle alter the anatomic features to a considerable degree; the same is true also of pregnancy and lactation.

Careful and practiced palpation affords one of the most valuable means of diagnosing lesions of the mammary gland. Preceded by an accurate history and preliminary inspection of the breasts under proper light, palpation translates changes in the skin or nipples, i. e., superficial irregularity, into specific underlying alteration of the tissues. This is best accomplished by lightly and delicately passing the finger tips radially over the entire breast by quadrants, from areola to periphery. A circumscribed tumor can usually be accurately outlined. Its mobility in relation to the tissues immediately adjacent aids in differentiating a discrete from an invasive neoplasm. Diffuse nodularity (adenomatosis) not infrequently can be distinguished from cyst formation, and gentle pressure along the ducts will occasionally express from the nipple secretions that in themselves are more or less diagnostic.

The axillary and clavicular areas, as well as the borders of the pectoralis and latissimus dorsi muscles, should be carefully palpated for involvement of the regional lymph nodes.

The posture of the patient during examination is extremely important. Frequently a "mass" felt between the thumb and fingers when the patient

36. Frank, R. T.: The Present Status of the Female Sex Hormone from the Clinical Standpoint. New York State J. Med. **34**:1009 (Dec. 1) 1934. Neustaedter.[19f] Frank, Goldberger and Spielman.[20]

is sitting and the breast is pendulous will disappear when the patient is prone and the breast is allowed to flatten itself to a "neutral disk" against the chest wall.

A combination of the three methods—transillumination, roentgenographic examination and palpation—may be necessary. These should be combined with a thorough general physical examination, special attention being given to possible pelvic disorders. A careful menstrual history must be included in each case.

A characteristic feature of this disease is the simultaneous occurrence of two or more lesions in the same breast. These include papillomatous cyst, blue dome cyst, adenoma, adenofibroma, cystadenoma and carcinoma. Microscopic study of repeated frozen sections from different areas is clearly indicated in such cases.

Bloodgood [37] suggested analysis of the contents of the various lesions as a means of differentiation. He pointed to the presence of blood as indicative of papillomatous cyst or of carcinomatous cyst and to its absence in blue dome cyst. Another distinguishing feature is the fact that the blue dome cyst is never grumous, as is the carcinomatous cyst, nor does it contain pus as does the tuberculous abscess or the abscess associated with chronic lactational mastitis.

A bloody or serous discharge from the nipple, while not a frequent occurrence, may likewise serve as a diagnostic aid. From a study of records of patients with mammary disease who had been treated for several years, Stowers [38] found that a discharge of blood from the nipple, with no palpable tumor and with no history of trauma, presumably indicates a papilloma of a duct or ducts of the breast. A so-called purulent discharge from the nipple in his series was associated with "cystiphorous desquamative epithelial hyperplasia" or with carcinoma. A discharge of serum or blood from the nipple, with or without a papable tumor, points to a surgical condition.

In establishing the presence of "premalignancy" or "early malignancy," biopsy must be undertaken. Of paramount importance is the question of "premalignancy." Features such as highly atypical shape, size and staining power of the proliferating gland and duct cells, solid nests in the lumens, connective tissue increase subdividing the bands of epithelium without true invasion of the connective tissue by the neoplasm or the occurrence of numerous mitoses are frequently considered as representing a premalignant phase. Some [26] are of the opinion, how-

37. Bloodgood, J. C.: The Blue-Domed Cyst in Chronic Cystic Mastitis: Its Relation to the Cure of Cancer, to Benign Lesions of the Breast, and to the Educational Program, J. A. M. A. **93**:1056 (Oct. 5) 1929.

38. Stowers, J. E.: The Significance of Bleeding or Discharge from the Nipple, Surg., Gynec. & Obst. **61**:537 (Oct.) 1935.

ever, that there is no indication that a picture representing these features definitely precedes cancer of the breast. The term "premalignant" has been so greatly abused that many pathologists avoid its use if the microscopic picture as described in such a disease is caused by abnormal endocrine influences. "Premalignant" indicates that there is growth activity of the epithelial cells and that the fibrocystic disease is serious. Accurate statistics are lacking, but Aschoff [6] was "persuaded that a precancerous state degenerates into carcinoma in the course of years, not decades . . . ." If, however, the hyperplastic epithelium extends into the surrounding connective tissue stroma, disturbing the normal outline of the base of the epithelial cells against the stroma, the condition is definitely carcinoma. What is usually called "early malignancy" is carcinoma which has not grown extensively. It may have been growing slowly. Hence, "early" is highly inappropriate. It is the breakdown of the usual restrictions of tissue order or structure which indicates malignancy. Carcinoma and fibrocystic disease may both be present, and it is generally necessary to examine several sections before the carcinoma is located.

TREATMENT

Considering the varied nature of the symptoms and the pathologic and anatomic picture that may be presented, as well as the fact that a definite etiologic basis for fibrocystic disease is still unknown, it is obvious that treatment must be adapted to the individual case.

When pain is the predominant symptom and is confined to the upper limits of the breast (pain due to actual weight or drag of a pendulous breast) adequate support or uplift will generally provide prompt relief. In other cases removal of foci of infection will often result in improvement of the mammary condition. Roentgen irradiation of the ovaries may be of benefit, although this method is applicable only to a limited group. Diathermy, short wave therapy and moist heat have received comparatively little attention.

When pelvic disorders occur in association with fibrocystic disease the pelvic condition should be treated first. Many patients require no other therapy, the mammary condition soon responding to improvement or cure of the pelvic condition. A similar interdependence exists throughout the entire endocrine system, the thyroid, parathyroid, pituitary, adrenals, ovaries and mammary glands, among others, being directly or indirectly included. In case of amenorrhea of thyroid origin accompanied by fibrocystic disease, thyroid substance will, as a rule, favorably influence the amenorrhea [39] and, in turn, will often entirely

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39. Novak, E.: The Therapeutic Use of Estrogenic Substances, J. A. M. A. **104**:1815 (May 18) 1935.

clear up the fibrocystic disease. Amenorrhea, however, does not in all cases respond to this form of glandular therapy.

Other forms of glandular therapy have been advocated, from time to time, for the treatment of fibrocystic disease.[40] Corpus luteum, which had previously been employed in eliminating or ameliorating disagreeable symptoms of the menopause, was administered two decades ago[41] for the treatment of mammary pain accompanying menstruation. Cutler[42] from an opposite point of view, concluding that the condition of "painful breasts" is due to overstimulation by the corpus luteum, administered ovarian residue by mouth for the purpose of increasing the deficient follicular and interstitial elements of the ovary and thus counteracting the overactive corpus luteum. Whitehouse[13] for the same purpose of counteracting the corpus luteum and, in addition, of preventing mammary stagnation administered an estrus-producing substance, estrone (theelin) daily by injection during the premenstrual period. Lewis and Geschickter[12b] recently reported the successful treatment of "painful breasts," the condition being characterized by them as an early stage of cystic disease. An estrogen was given intramuscularly twice a week for several months. Although favorable results were obtained in "adenosis," lasting results in the presence of cysts were more difficult to obtain.

I have tried treating patients with fibrocystic disease by various means. The oral administration of ovarian residue, as advised by Cutler,[42] was disappointing. Few, if any, similar substances were of value when given orally, inasmuch as the action of the gastric juices on them makes exact dosage impossible. The hypodermic administration of a gonadotropic substance from the placenta (A. P. L.) has given the most favorable results, producing relief of pain and subsidence of palpable alterations in the breast.

Discrete masses, solid or cystic, should be removed surgically by simple excision of the mass. When not obviously benign or grossly malignant, the neoplasm should be subjected to immediate histologic (frozen section) examination to determine the necessity for more extensive surgical treatment. Diffuse fibrocystic involvement of one or both breasts, however, does not lend itself so readily to multiple excisions. Owing to the widespread distribution of the process as demonstrated by serial sections, total ablation of mammary tissue (simple

40. Goodman, B. A.: Glandular Therapy in Diseases of the Breast, S. Clin. North America **12**:539 (April) 1932.

41. Lisser, H.: A Note on the Use of Corpus Luteum to Prevent Painful Breasts of Menstruation, Endocrinology **2**:12 (Jan.) 1918.

42. Cutler, M.: Cause of "Painful Breasts" and Treatment by Means of Ovarian Residue, J. A. M. A. **96**:1201 (April 11) 1931.

mastectomy) is sometimes necessary. When possible, however, opportunity should be given for other measures, especially endocrine therapy, to prove their inadequacy before resorting to operation.

SUMMARY

1. The term "fibrocystic disease of the breast" is suggested to cover and possibly to replace the diverse terms applied to a group of conditions referred to as abnormal involution of the breast, cystic disease of the breast, Reclus' disease, serocystic tumor of the breast, chronic cystic mastitis, cystadenoma, Schimmelbusch's disease, senile parenchymatous hypertrophy, mazoplasia, cystiphorous desquamative hyperplasia, cystoplasia, cystic disease of the breast, mastopathia, adenofibrosis and fibroadenomatosis. The choice of the term "fibrocystic disease of the breast" rests on its definite characterization of the outstanding features of the condition—the fibrous and cystic elements.

2. The disease is a nonstatic condition the clinical and microscopic pictures of which are varied.

3. That fibrocystic disease of the breast is in the beginning essentially a functional disorder of the nonlactating breast, which assumes certain pathologic characteristics as a result of repeated and possibly aberrant stimulation by the luteal hormone progestin and the associated hormones estrogen and prolactin (the lactogenic substance of the anterior lobe of the pituitary) is a tenable hypothesis. If one accepts the stagnation theory of Keynes,[31] it is possible to trace a series of events beginning with proliferation in the breast, including cyclic changes produced by menstruation and lactation. and continuing through the various states of the disease—the cystic and papillomatous stages and, possibly, a malignant stage.

4. Treatment in each case must include a careful history, a period of competent observation and elimination of focal infection and concomitant pelvic disorders. In many cases treatment with potent estrogenic substances has proved efficacious. A chorionic derivative (anterior pituitary-like principle) seems at present to be most effective.

5. Continued investigation of the interrelations of the endocrine glands and qualitative and quantitative determinations of the various endocrine substances are essential, for therein lies the promise of a better understanding of the pathologic processes involving the human breast.

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RATE OF FIBROPLASIA AND DIFFERENTIATION IN THE HEALING OF CUTANEOUS WOUNDS IN DIFFERENT SPECIES OF ANIMALS

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In the healing of wounds of muscle, fascia, skin and gastric wall of the dog, strength returns in a definite manner. During the first four days, the wounds have only the strength contributed by the sutures and the adhesion of the wound surfaces; subsequently, however, strength mounts rapidly, reaching a maximum on the twelfth to the fourteenth day of healing.[1] This increase in strength is accompanied microscopically by regeneration of fibrous tissue; hence, strength is used as an index to the rate of fibroplasia. Because the rate of fibroplasia is the same in the healing of these diversified anatomic structures, it has occurred to us that the rate should be studied in the healing of wounds of one tissue in several species of animals. In this way any influence on the rate of fibroplasia due to differences in species could. be determined. In the experiments described here, therefore, the relation of species differences to the rate of fibroplasia has been studied by testing the strength of healing wounds in the skin of the usual laboratory animals. Particular attention has been directed toward the question whether the wounds actually return to the original strength of the skin injured.

METHOD

Under strictly aseptic precautions, wounds approximately 4 cm. in length were cut in the skin of the abdomens of anesthetized rats, guinea pigs, rabbits, cats and dogs. The ends of each wound were marked subcutaneously with silk to indicate the extent of the wound when the tissues should be removed. The edges were approximated with interrupted A silk sutures, subsequently removed after a week of healing (or earlier when the strength of the wound was determined earlier).

1. Howes, E. L.; Sooy, J. W., and Harvey, S. C.: The Healing of Wounds as Determined by Their Tensile Strength, J. A. M. A. 92:42 (Jan. 5) 1929.

The wounds were periodically inspected for infection, and only those healing per primam were ever tested for strength. For the test a strip of tissue was excised at right angles to the wound. This strip was of no greater width than the length of the wound. It was cut sufficiently long so that it might be secured in the clamps of the tensile strength machine. The thickness and width of each wound were measured after the strip was put under a tension of 100 Gm. in the tensile strength machine.[2] Tests of strength were made every day or every other day during

Table 1.—*Breaking Strength of Cutaneous Wounds*

Guinea Pig			Rat		
Day	Number of Animals	Av. in Gm. per Sq. Mm.	Day	Number of Animals	Av. in Gm. per Sq. Mm.
4	2	0	3	4	1
6	1	45	4	4	6
7	3	37	5	45	15
8	1	151	6	4	23
9	2	99	7	2	40
10	1	137	8	3	98
14	1	155	10	44	99
16	2	102	12	2	148
20	3	174	13	3	157
22	1	114	14	4	143
24	1	162	15	39	115
26	2	124	17	2	134
28	2	139	18	3	163
30	1	186	20	12	203
33	2	301	22	3	299
35	2	187	24	4	417
36	1	564	27	4	450
38	2	283	30	34	573
40	2	309	32	2	472
60	1	1,723	34	2	608
65	1	333	35	1	579
70	1	470	36	6	656
143	1	1,253	37	1	830
200	1	2,225	38	2	778
250	2	1,994	40	33	572
			42	3	800
			45	4	885
			50	31	791
			52	2	694
			53	2	1,007
			56	2	855
			58	2	782
			60	2	1,261
			64	2	1,052
			67	2	1,441
			70	2	1,036
			74	1	1,709
			77	2	745
			80	19	999
			90	1	1,516
			100	2	1,440
			127	1	1,314
			152	2	1,684
			178	1	1,232
			210	2	2,092

the first twenty days of healing but at less frequent intervals in the subsequent weeks. The strength of the wound was calculated for a unit of area (tables 1

2. The measurement of the tissues presented a problem. If the width of the wound was measured in situ, thickness could not be measured accurately, and small variations in this diameter markedly affected the results. On the other hand, if the tissue was removed, the tension applied to the strip and its direction of application changed the dimensions. However, with the same distortion applied to each strip, measurements were obtained of sufficient accuracy to allow a comparison of the results.

and 2) ; the corrected strengths were plotted as a function of time. The resulting curves are shown in figures 1 and 2. At frequent intervals the character of healing was studied microscopically and correlated with the changes in strength of the wound. Normal skin from the different animals was also tested for strength and cut for microscopic study.
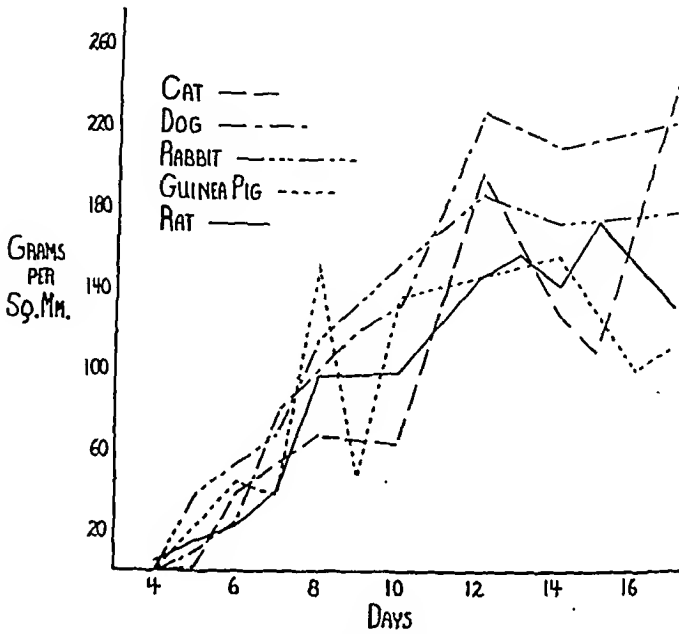
Fig. 1.—Early breaking strength of cutaneous wounds.
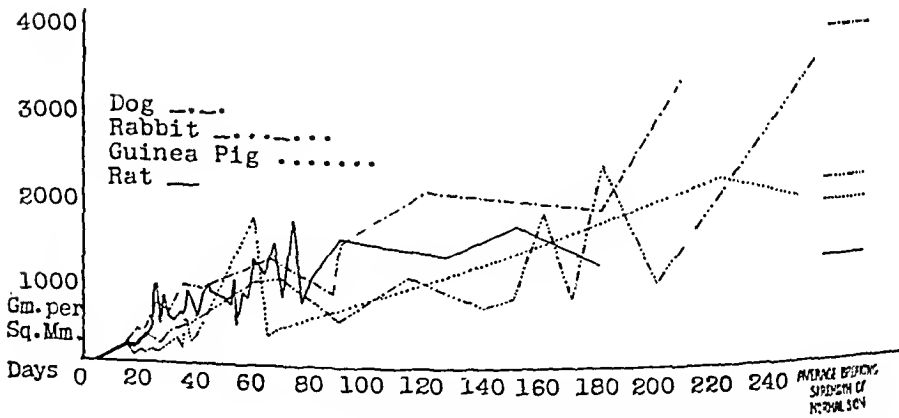
Fig. 2.—Later breaking strength of cutaneous wounds.

STRENGTH OF NORMAL SKIN

The strength of the normal skin of different animals is shown in table 3. The variation in strength was not all caused by error in the method of testing, for it occurred in a distribution typical of biologic variations. The amount of variability occasioned by the method can be approximated from an inspection of the first five values in the table.

for the rat, all obtained from the same skin. The greater average strength of the skin per unit of area occurred in the larger animals. In general, skin has a fair degree of strength, a physical property in consonance with its function as protector of the organism from the environment. The data furnished by Gratz [3] allow a comparison of the strength of the skin with that of other fibrous structures of the body. He has shown that tendon and fascia in the dog have an average strength of about 5,000 Gm. per square millimeter, while that of the skin of the same animal, from our experience, is approximately 4,000. The

TABLE 2.—*Breaking Strength of Cutaneous Wounds*

Rabbit			Dog			Cat		
Days	No. of Animals	Av. in Gm. per Sq. Mm.	Days	No. of Animals	Av. in Gm. per Sq. Mm.	Days	No. of Animals	Av. in Gm. per Sq. Mm.
5	2	30	4	1	0	5	3	2
7	3	68	5	3	10	6	1	89
8	2	115	6	1	23	8	6	68
10	3	154	7	1	80			
12	2	188	9	1	120	12	4	200
14	5	175	10	2	183	14	2	129
17	2	181	12	2	230	18	1	493
19	1	193	14	4	213	20	1	348
22	1	320	17	1	225	30	1	532
27	1	236	19	1	415			
30	1	342	21	1	376			
40	1	509	26	1	721			
60	1	969	30	1	602			
70	1	1,018	35	1	930			
80	1	794	42	1	880			
90	1	537	66	1	1,275			
100	1	779	87	1	871			
115	1	1,062	90	3	1,430			
120	1	1,627	120	1	2,068			
140	1	709	180	1	1,552			
150	1	827	207	1	3,348			
160	1	1,784	345	1	2,223			
170	1	801	353	1	1,589			
180	1	2,356	358	1	2,271			
200	1	1,022						
255	1	3,595						

strength of the skin is in the main derived from the corium, which is composed of heavy collagenous fibers intertwined and running in many directions (figs. 3 and 4).

COMPARISON OF STRENGTH OF THE HEALING WOUND IN VARIOUS SPECIES

In all the wounds, strength began to mount on the fifth day and continued to increase at the same rate, slowing to reach a maximum on

3. Gratz, C. M.: Biomechanical Studies of Fibrous Tissues Applied to Fascial Surgery, Arch. Surg. **34**:461 (March) 1937.

TABLE 3.—*Breaking Strength of Normal Skin in Grams per Square Millimeter*

Rat		Guinea Pig	Rabbit	Dog	Cat
950	414	1,136	2,273	2,591	6,427
1,045	755	3,123	2,841	4,127	4,036
1,227 }*	468	1,075	2,300	3,195	2,968
1,090	400	1,223	1,700	4,777	3,541
1,272	845	2,023	2,436	3,364	7,736
1,323	873	1,914	1,700	4,364	3,636
	1,218	2,550	1,331	3,168	6,563
2,273	1,077	1,432	3,050	3,009	8,471
1,845	1,014	1,541	2,041	2,504	4,300
2,165	741	1,182	2,050	1,873	5,891
2,000	1,077	2,254	1,218	6,627	4,545
1,277	664	1,791	2,841	5,491	6,059
1,818	627	2,727	1,590	5,554	5,191
1,364	1,705	2,145	1,705	3,304	1,109
1,555	1,295	1,373	1,091	4,091	5,150
1,464	995	1,859	3,500	7,805	5,495
1,273	1,259	1,664	2,045	3,445	12,063
1,136	1,595	1,973	1,955	4,341	8,413
864	1,495	1,173	2,636	3,650	9,259
1,559	2,368	1,814	2,423	7,727	.....
704	1,623	414	1,577	2,709	.....
291	673	2,172	1,590	3,000	.....
1,150	1,205	45	6,759	4,759	.....
1,318	1,618	50	1,532	3,468	.....
982	1,486	2,186	3,359	.....	.....
295	1,795	1,281	3,818	.....	.....
668	1,814	2,000	1,627	.....	.....
890	1,818	990	1,418	.....	.....
964	2,650	1,350	1,854	.....	.....
1,623	1,559	1,400	2,704	.....	.....
1,364	2,600	695	422	.....	.....
.....	.....	227	.....	.....	.....
.....	.....	1,577	.....	.....	.....
.....	.....	605	.....	.....	.....
.....	.....	1,545	.....	.....	.....
.....	.....	1,514	.....	.....	.....
.....	.....	981	.....	.....	.....
.....	.....	2,231	.....	.....	.....
.....	.....	1,481	.....	.....	.....
.....	.....	5,490	.....	.....	.....
.....	.....	6,627	.....	.....	.....
.....	.....	5,554	.....	.....	.....
.....	.....	3,304	.....	.....	.....
Mean...........	1,254	1,909	2,127	3,931	5,858 Normal average
Standard deviation of mean.	68	172	190	309	574

* From the same animal.

TABLE 4.—*Breaking Strength of Cutaneous Wounds at End of Fibroplasia in Grams per Square Millimeter*

Rat at 15 Days		Guinea Pig at 14 Days	Rabbit at 14 Days	Cat at 14 Days	Dog at 14 Days
195	136	95	264	159	182
91	209	245	377	105	255
105	227	127	254	114	260
155	191	...	91	...	216
100	318	...	95	...	141
191	77	...	132	...	227
214	182	...	214	...	314
277	227	...	164	...	165
273	164	...	105	...	...
205	130	...	45	...	...
136	136	...	205	...	...
91	116	...	155	...	...
141	241	...	...	...	...
282	128	...	...	...	...
77	173	...	...	...	...
118	179	...	...	...	...
182	195	...	...	...	...
201	136	...	...	...	...
156	102	...	...	...	...
236	...	...	...	...	...
Mean	175	156	175	125	157
Standard deviation of mean	9.9	37.1	13.7	17?	
Variations in average......	15.4	152	190		127
Calculated with standard deviation..................	16.6	119	160	112	
Percentage of original strength.............	13	8	8	2	5

the twelfth to the fourteenth day of healing (fig. 1). The rate of fibro-plasia was not affected by differences in species. At the end of the period of fibroplasia the normal strength of the skin was not regained. In the rat, 13 per cent of the strength was restored, in the rabbit 8 per cent, in the cat 2 per cent and in the dog 5 per cent (table 4). The percentage variations in strength resulted more from the difference in the original strength of the skin injured than from the difference in the strength of the new fibrous tissue. The spread of original strength of the skin is compared with the grouping of the strength of the wounds in figure 2. This grouping suggests that the tissue produced by fibro-
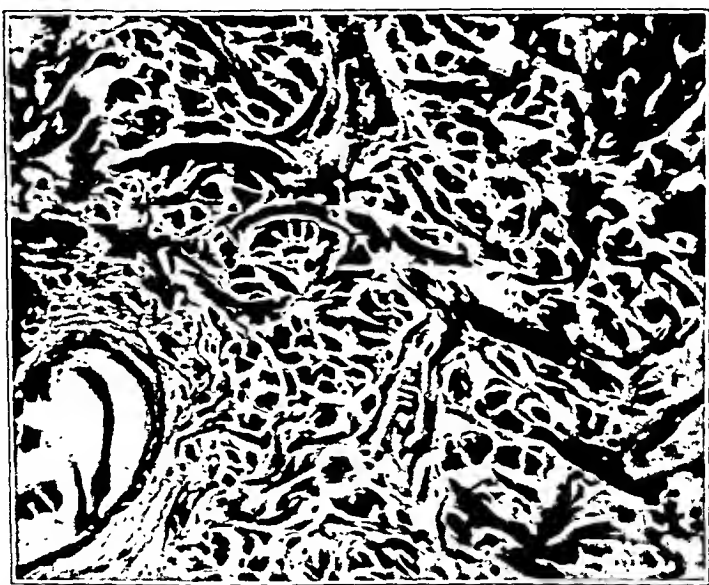
Fig. 3.—Collagenous fibers (× 200) of the normal corium of the rat.

plasia has the same strength per unit of area. In each wound the tissue was relatively undifferentiated, was of homogeneous density and was composed of fine parallel fibers with numerous fibroblasts between. It was vascular and had a loose arrangement of stroma (figs. 5, 6 and 7). The average strength in each wound, with the possible exception of that of the dog, was within the range of error of the experiment.

The anatomic explanation as to why the wound had not returned after the process of fibroplasia to the original strength of the skin injured was found in the difference between the embryonal-like tissue produced by the process and the well differentiated, heavy and compact collagenous fibers of the original corium (figs. 3 and 4).

A secondary rise in strength of the cutaneous wounds of the different animals occurred at approximately the same time in each. It is present on the twentieth day in the rat, on the twenty-second day in the rabbit and on the eighteenth day in the cat, and although earlier experiments[1]
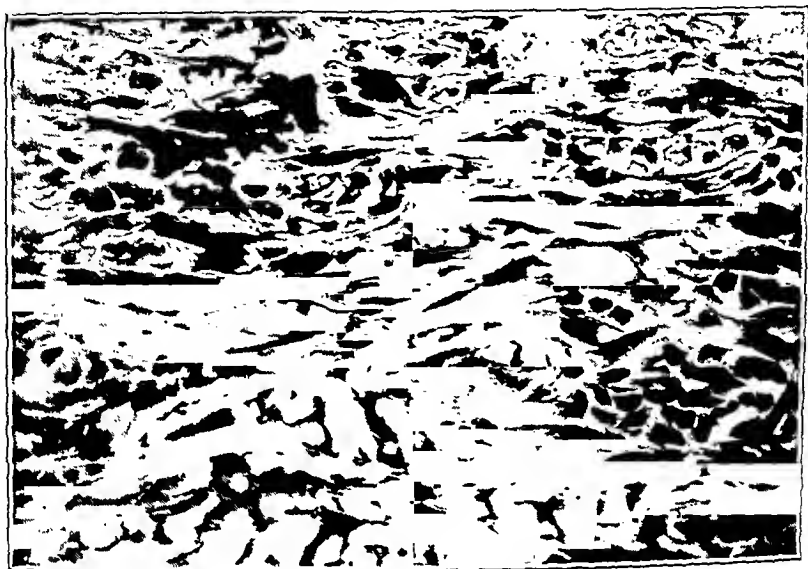
Fig. 4.—Collagenous fibers (× 200) of the normal corium of the dog.
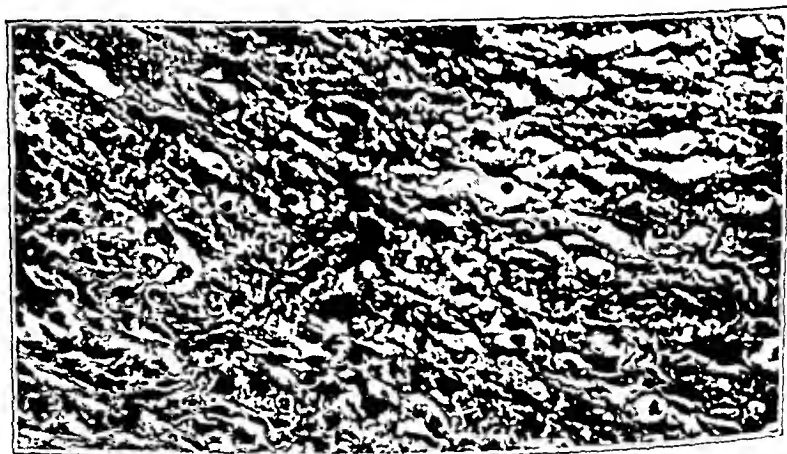
Fig. 5.—Fibrous tissue (× 200) resulting from fibroplasia. A dog was used in this experiment. The photomicrograph was taken when the wound was fourteen days old.

suggested that the rise might occur later in the wound of the dog, it appeared in this animal on the nineteenth day. On the other hand, in the wound of the guinea pig it was delayed until the thirtieth day.[4]

4. The guinea pig was found to be the poorest laboratory animal for these experiments. The usual percentage of wounds healing per primam was n't obtained with this animal.

Through this secondary rise in strength, the scars [5] ultimately regain approximately the original strength of the skin injured (fig. 2). This secondary increase in strength is accompanied anatomically by an organizing differentiation of the primary tissue produced by the fibroplasia.
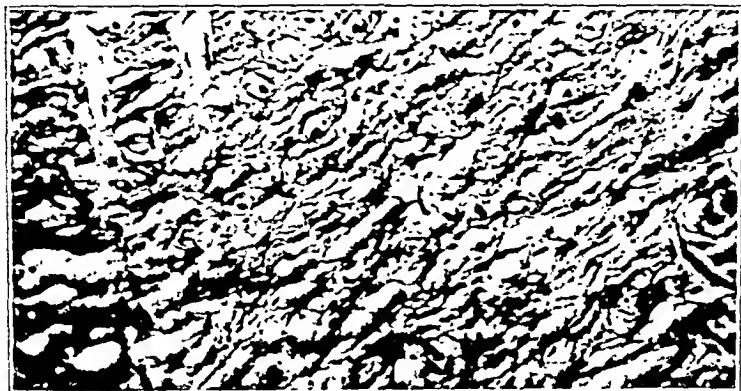
Fig. 6.—Fibrous tissue (× 200) resulting from fibroplasia. A rat was used in this experiment. The photomicrograph was taken when the wound was fourteen days old.
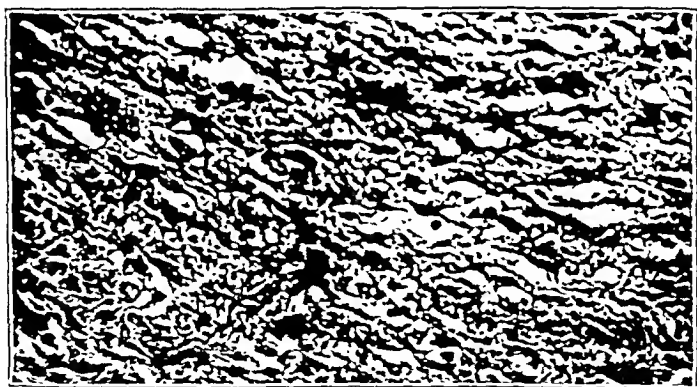
Fig. 7.—Fibrous tissue (× 200) resulting from fibroplasia. A guinea pig was used. The photomicrograph was taken when the wound was fourteen days old. The round spots are not fibers cut in cross section but lymphocytes.

The fine fibrils increase in size, and more of them run in directions other than parallel (figs. 8, 9 and 10). The sizes of the collagenous

5. "Scar" seems the proper word at this time, for the wounds are healed in the usual sense of the term.

fibers more and more approximate but never equal the dimensions of those of the original corium. The round cells and blood vessels of the primary tissue gradually disappear. Fewer elastic fibers are present,
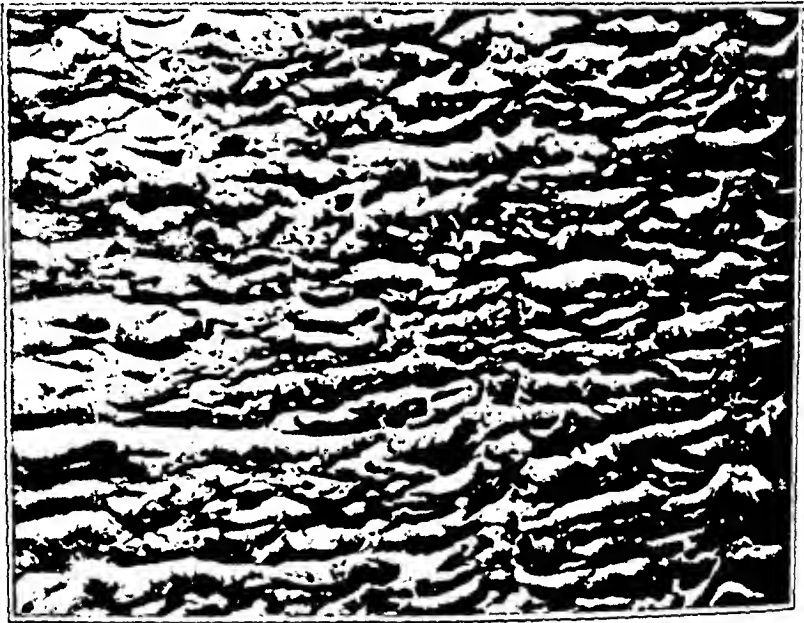
Fig. 8.—Fibrous tissue (× 200) of the scar of a fifty-one day old wound. A rat was used.
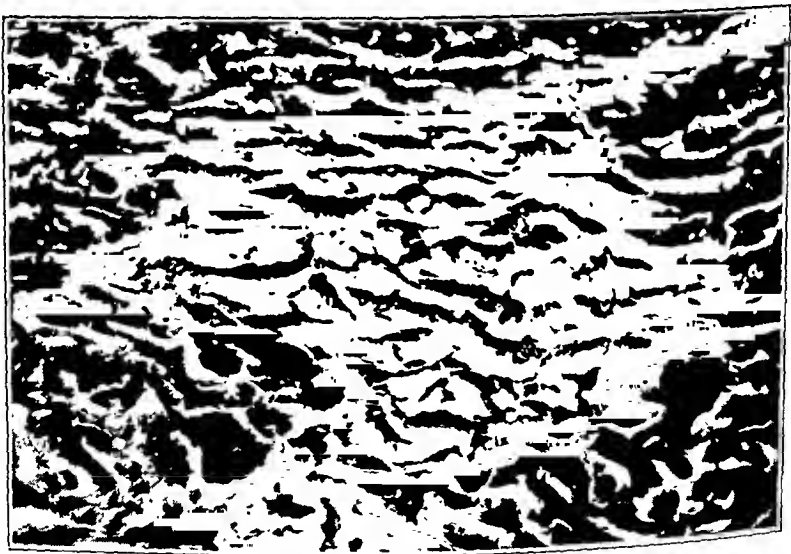
Fig. 9.—Fibrous tissue (× 200) of the scar of a ninety day old wound. A guinea pig was used.

and these are short and thick. The entire architecture is differentiated without a vestige of embryonal pattern. The collagenous fibers, however, are more rudimentary and more compact than in the original
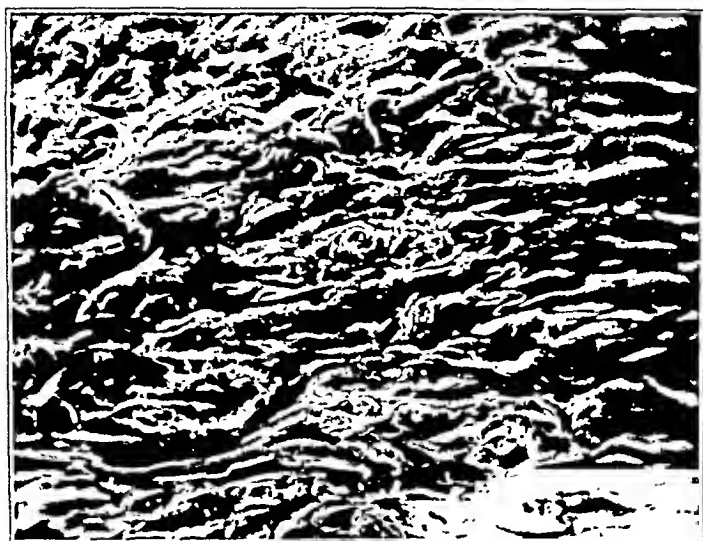
Fig. 10.—Fibrous tissue (× 200) of the scar of an eighty-two day old wound. A rat was used.
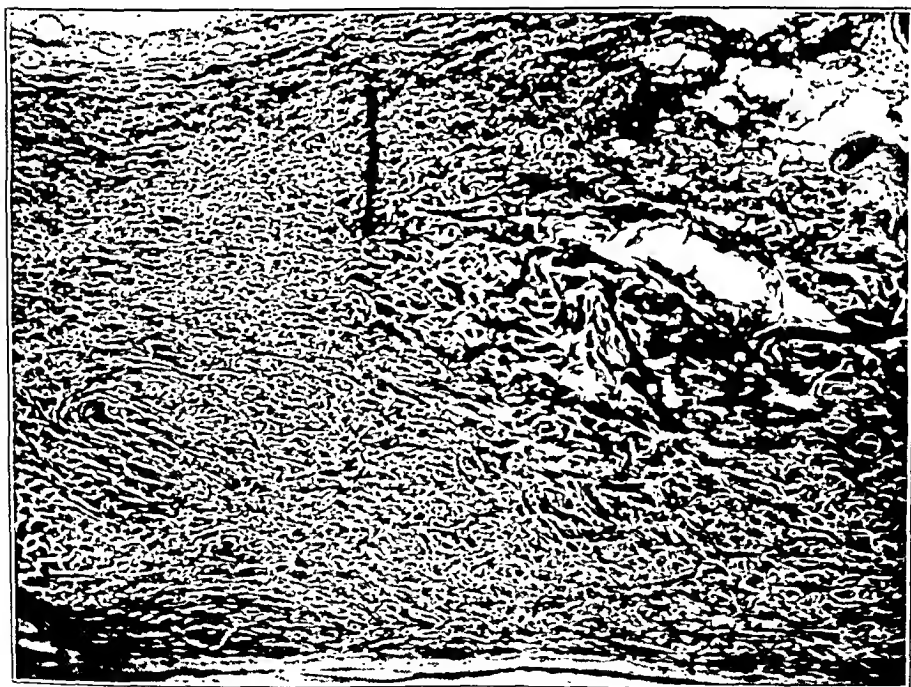
Fig. 11.—Scar left by the experimental wound (× 95). Note the normal corium at the right. The experimental animal was a rat. The photomicrograph was taken one hundred and fifty-eight days after the experiment.

corium, and the picture does not completely resemble the normal but closely approximates it (fig. 11).

The rate of differentiation, as judged by the increase in the strength of the scars per unit of area, is not of unusual velocity in any particular species (fig. 2). Yet the original strength of the skin is regained after varying lengths of time. These variations must be attributed to the differences in the ultimate strength to be regained. For example, with differentiation proceeding at the same rate in the scars of the rat, the rabbit and the guinea pig and the ultimate strength needed being 1,200 Gm. per square millimeter in the skin of the rat, 2,170 Gm. in the rabbit and 3,930 Gm. in the dog, it is understandable that the strength of the scar becomes as great as that of normal skin after sixty days in the rat and after one hundred and eighty days in the rabbit and that after three hundred and fifty-eight days the original strength is not completely regained in the scar of the dog (tables 1, 2 and 3 and fig. 2).

COMMENT

The character and rate of fibroplasia were the same in the healing of cutaneous wounds of the different species of animals studied. From the results obtained, together with the previous data on the character and a similar rate of fibroplasia in the healing of wounds of different tissues of the same animal,[1] the conclusion must be reached that the process of fibroplasia is an independent biologic phenomenon unrelated to the kind of tissue or the species wounded and corresponding to the general laws of growth. This has been discussed elsewhere.[6]

The more rapid gain of strength after the period of fibroplasia in the healing of wounds in the smaller animals has given origin to the concept that their wounds heal faster than do those of larger animals. Actually, however, the greater gain is accomplished not because of an increased rate of fibroplasia and differentiation but because less strength is ultimately needed to reach the normal.

While the normal strength of the skin is not regained in the period of active fibroplasia, the original strength of muscle, gastric wall and fat is so restored.[1] The reason for this is that the normal strength of these structures is no greater than that developed by proliferation of fibroblasts alone, while in structures such as skin, bone, tendons and fascia an organizing differentiation is required for a restoration of the much greater normal strength. Thus, the healing of structures originally possessing greater strength than the tissue regenerated by fibroplasia is accomplished by the generation of a "primary callus," which rapidly establishes the continuity and which must be differentiated later to

6. Harvey, S. C.: Reaction to Injury as a Function of Growth, Proc. Inst. Med. Chicago **10**:70 (April 15) 1934.

approximate the original function. The excess of primary tissue disappears with differentiation, but wounds healing in this manner remain comparatively weak until differentiation is completed. The more strength the tissue possesses originally, the longer will be the period of relative weakness.

CONCLUSIONS

1. The rate of fibroplasia is the same in the healing of cutaneous wounds in the rat, the guinea pig, the rabbit, the dog and the cat, and the difference of species does not affect the rate.

2. The period, approximately two weeks, during which fibroplasia occurs is an independent biologic phenomenon unrelated to the species or type of tissue wounded and corresponds to the process of growth.

3. The tissue of the wound does not return to the normal strength of the skin except by a prolonged period of differentiation of the tissue produced in this initial period.

4. The velocity of differentiation as estimated by the secondary increase in the strength of the wound is the same for the different species of animals investigated.

5. Nevertheless, the time when the scars attain the original strength varies in different animals. The variations are occasioned by differences in the strengths which have to be attained in order to reach the normal, and are therefore dependent on the varying normal strengths in the animals involved.

INJURIES OF THE LIGAMENTS OF THE KNEE JOINT

AN EXPERIMENTAL STUDY

M. THOMAS HORWITZ, M.D.

PHILADELPHIA

There has been substantial clinical proof in the past few years that the cruciate ligaments play a role secondary to that of the collateral ligaments in preservation of the stability and function of the knee joint. As I have noted in a previous communication,[1] several observers have shown that a torn anterior cruciate ligament may be disregarded or a fractured tibial spine and anterior cruciate ligament excised without marked impairment of the integrity of the knee joint, provided the collateral ligaments are intact. This fact has led some authors (Bennett,[2] Milch[3]) to undertake successfully the repair of the collateral ligaments alone, disregarding the associated tears of the cruciate ligament.

This concept, at variance with the teachings of most anatomists, was corroborated anatomically by me[4] after a study of the knee joints of human cadavers at the Daniel Baugh Institute of Anatomy in Philadelphia. The collateral ligaments were noted to be the structures most essential to preservation of the intrinsic stability of the extended knee, inhibiting lateral and rotatory motion of the tibia on the femur. In the absence of the cruciate ligaments, the internal lateral ligament, especially through its anterior portion, which remained taut in flexion, efficiently checked internal rotation, anteroposterior motion and distraction of the tibia from the femur in the flexed knee. Both cruciate ligaments, contrary to usual teachings, were most tense in flexion and internal rotation of the tibia on the femur. Their action was found to be accessory to that of the collateral ligaments and not indispensable to the stability of

1. Horwitz, M. T., and Davidson, A. J.: Newer Concepts in the Treatment of Injuries of the Ligaments of the Knee Joint: An Evaluation of the Mauck Operation, Surgery 3:407, 1938.

2. Bennett, G. E.: Relaxed Knees and Torn Ligaments, Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America 6:351, 1931.

3. Milch, H.: Injuries to the Crucial Ligaments, Arch. Surg. 30:805 (May) 1935.

4. Horwitz, M. T.: An Investigation of the Surgical Anatomy of the Ligaments of the Knee Joint, Surg., Gynec. & Obst. 67:287, 1938.

the knee joint. Experimental tears of the cruciate ligaments without associated fractures (except of the tibial spine) were best obtained in the human cadaver by forcibly abducting the tibia on the femur, with the knee and hip joints flexed and the pelvis fixed, and occurred only after the internal lateral ligament had also given way (Pringle[5]). The frequent association of injuries to the collateral and cruciate ligaments of the knee joint and often of the meniscuses as well has been observed clinically.

HEALING OF DEFECTS OF THE COLLATERAL AND CRUCIATE LIGAMENTS

It has been reported that acute tears of the cruciate ligaments, as in total dislocations of the knee joint, will be repaired by simple immobilization of the knee in full extension. In the light of the aforementioned anatomic findings and of the experimental evidence to follow, it is suggested that the restoration of stability to severely traumatized knee joints by such conservative methods is due rather to the repair of associated tears of the collateral ligaments.

METHODS OF INVESTIGATION AND RESULTS

Group 1.—In 8 rabbits under ether anesthesia, longitudinal incisions were made directly over the inner aspect of the left knee. The internal lateral ligament was exposed and was incised transversely through part of its thickness just above the joint line; the tear was completed and enlarged by forcible abduction of the tibia on the femur. In 2 instances, a ¼ inch (0.6 cm.) segment was excised from the internal lateral ligament. The skin was sutured with black silk, and in 4 instances the leg was immobilized in plaster bandage in fullest extension (about 150 degrees), while in the remaining instances no fixation was employed. The rabbits were killed at periods varying from two to twelve weeks.

Healing in various stages was noted in each specimen. When the defect was a simple incision and tear, the tendinous ends became adherent with coagulated plasma, while where large gaps were created by excising ¼ inch (0.6 cm.) of the internal lateral ligament, the interval became filled with coagulated blood and fibrin (fig. 1A). This was followed by replacement with soft fibrous tissue and then by formation of dense scar tissue, at first vascular and red and later white (fig. 1B and fig. 2BE). Histologically the process of repair was that normal to connective tissue (Boyd[6]), the primary scaffold of coagulated blood and fibrin being penetrated by proliferating young fibroblasts and vascular endothelial buds from the open tendinous ends and from the adjacent

5. Pringle, J. H.: Avulsion of the Spine of the Tibia, Ann. Surg. **46**:169, 1907.

6. Boyd, W.: A Textbook of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1934.
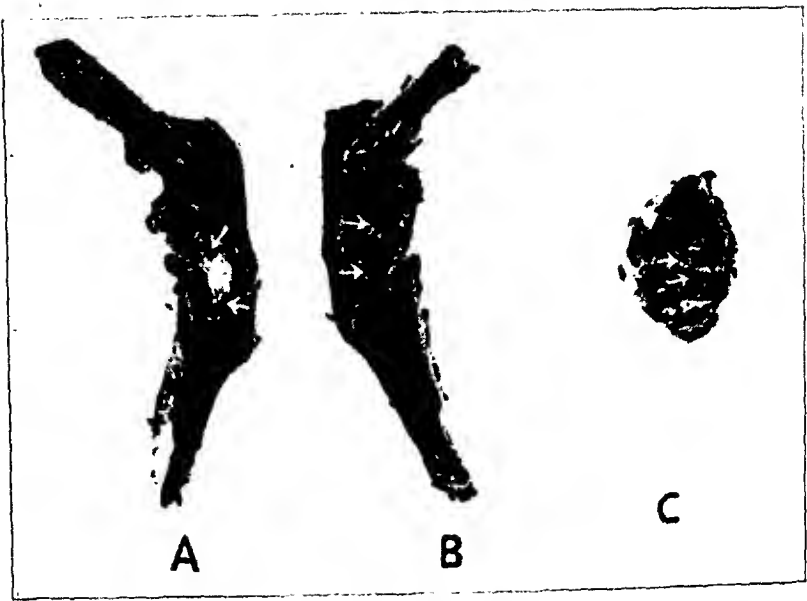
Fig. 1.—*A*, internal lateral ligament of the left knee of a rabbit, two weeks after excision of ¼ inch (0.6 cm.) of the ligament. A hemorrhagic clot has filled the gap between the ligamentous ends. *B*, internal lateral ligament of the right knee of a rabbit, three weeks after excision of ¼ inch (0.6 cm.) of the ligament. The gap is completely bridged by vascular connective tissue. *C*, anterior cruciate ligament of the right knee of a rabbit two weeks after division. The ligamentous ends are ununited and retracted.
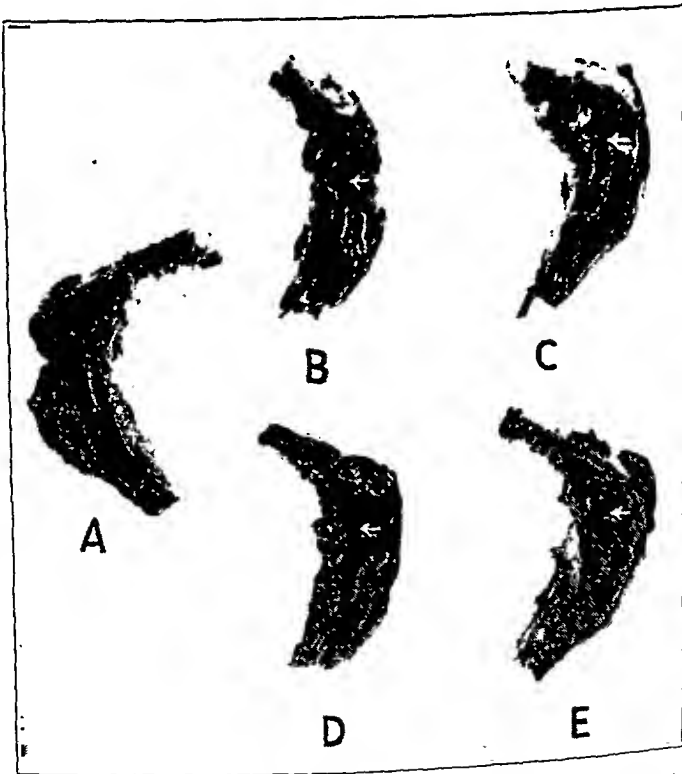
Fig. 2.—Internal lateral ligament. *A*, normal right knee (rabbit). *B* to *E*, left knees (rabbit six, eight, ten and twelve weeks respectively) after division of the ligament above the level of the joint line. Firm union is present in all specimens, the scar tissue being vascular and red in *B* and *C* and avascular and white in *D* and *E*.

tissues. At the end of three months the specialized connective tissue of the ligament had not completely replaced the scar tissue. This finding differs from the experience of Garlock,[7] who noted such complete substitution of the scar tissue in twenty-eight days after injury of the tendon.

Group 2.—In 8 rabbits under ether anesthesia, through a longitudinal incision between the patella and lateral femoral condyle of the right knee, the cruciate ligaments were severed with a tenotome, the anterior in 6 instances, the posterior in 1 and both in 1. The wound was closed with black silk and the extremity was encased in a plaster bandage with the knee at fullest extension (150 degrees). The rabbits were killed at periods varying from two to twelve weeks.
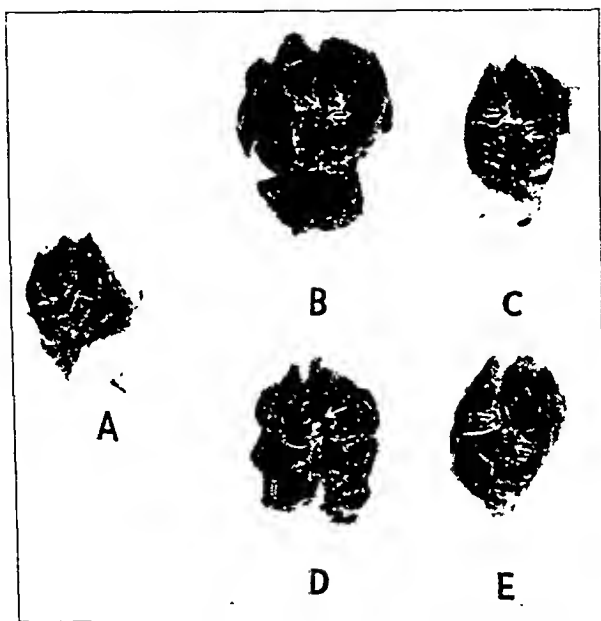
Fig. 3.—Cruciate ligaments. *A,* cruciate ligament of the normal left knee of a rabbit. *B, C, D* and *E,* right knees of rabbits, six, eight, ten and twelve weeks, respectively, after division of the anterior cruciate ligament in *B, C* and *E* and of the posterior in *D.* There is failure of union in all specimens, with retraction of the ligamentous ends in *B* and *D,* and gradual absorption of these stubs in *C* and *E.*

Union of the severed cruciate ligaments failed to occur in all specimens (fig. 1*C* and fig. 3*B, E*). In the early stages the joint was found filled with coagulated blood, fibrin and synovial fluid, and there was slight congestion of the synovial membrane and the infrapatellar

7. Garlock, J. H.: The Repair Processes in Wounds of Tendon and in Tendon Grafts, Ann. Surg. 85:92, 1927.

fat pad. As early as two weeks after the operation much of the joint reaction had subsided, and the ends of the severed ligament were so retracted that they could no longer be approximated (fig. 1C). In the later specimens, these ligamentous ends became frayed, further retracted and gradually absorbed, so that ultimately only small stubs remained at the bony attachments (figs. 3C and 3E).

COMMENT

Union of the internal lateral ligament was firm in each instance as early as six weeks after the injury, with or without immobilization, and no preternatural mobility could be elicited. The opportunities for primary union of simple tears of this ligament are excellent, the small gap being immediately bridged by reparative elements. Where a large gap exists, healing is also satisfactory, for the interval is filled by localized hemorrhage and by the formation of richly vascular granulation tissue.

Several reasons are advanced, from this study, to explain the invariable occurrence of nonunion of cruciate ligaments in laboratory animals despite adequate fixation:

1. Hemorrhage does not remain localized between the severed ends of the ligament but is immediately dispersed within the joint cavity.

2. This blood is diluted by combination with synovial fluid, the formation of which is stimulated by the articular trauma and by the blood extravasation itself.

3. The ends of the severed ligament lie free within the joint cavity and are kept apart mechanically by the joint effusion.

4. The ligamentous ends retract early and tend to "curl up," and eventually they absorb so that only stubs remain at the bony attachments.

Histologic sections of the internal lateral ligaments of the knee joints of well preserved cadavers, prepared for my use by Dr. Andrew J. Ramsay, reveal that the collagenous fibers are arranged in parallel and compact bundles, while interposed are small areas of loose connective tissue containing isolated vessels; the Weigert elastic tissue stain reveals only an occasional elastic fibril (fig. 4A). The cruciate ligament is made up of aggregations of collagenous fibers less uniformly arranged, and interposed are large areas of loose connective tissue containing many vascular channels and an abundant network of elastic tissue (fig. 4B).

The tendency for the severed ends of the cruciate ligament to retract and the failure of those of the internal lateral ligament to do so are explained in great part by this variation in elastic tissue content. The deficient vascularity of the collateral ligament is compensated by the abundant supply of the adjacent subsynovial tissue (joint surface)

Fig. 4.—*A*, section of the human internal lateral ligament, × 100. The Weigert elastic stain was used. Note the regular arrangement of closely packed bundles of parallel collagenous fibers. Small amounts of loose connective tissue are interposed, but few elastic fibrils were located. *B*, section of the human anterior cruciate ligament, × 100. The Weigert elastic stain was used. Note the abundant loose connective tissue interposed between less uniformly arranged bundles of collagenous fibers (not shown), with an abundant fine elastic tissue network.

and by that of the overlying connective tissues. The blood supply of the cruciate ligament, although richer than that of the lateral ligament, is poorly supplemented by that of the subsynovial tissue, which only partly covers it.

SITE OF RUPTURE IN TEARS OF THE COLLATERAL AND CRUCIATE LIGAMENTS

Group 1.—Four human (cadaver) knees were stripped of their soft tissues and of their muscular and tendinous attachments. With the knee joint fully
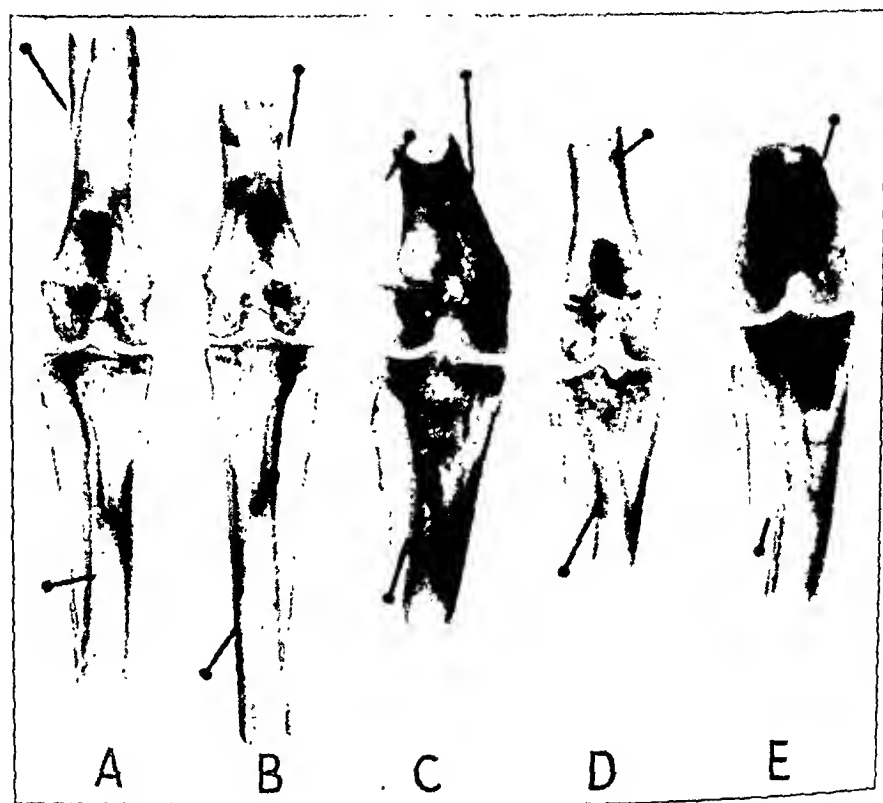
Fig. 5.—Roentgenograms of knees of rabbits, two weeks (*A* and *B*) to three months (*E*) after division of the internal lateral ligaments just above the level of the joint line. In no specimen is there evidence of pathologic calcification or ossification at the site of operation. The bony deposits at the femoral attachments of the ligament in specimens *A* and *B* probably represent small exostoses.

extended, the tibia was forcibly abducted on the femur until the internal lateral ligament was torn. This procedure was repeated, the hindlegs of two freshly killed rabbits being used.

In each instance the internal lateral ligament was seen to tear close to its bony attachment, in 3 of the human and in 2 of the rabbit specimens at the femoral attachment and in 1 of the human and in 2 of the rabbit knees at the tibial insertion.

Group 2.—In four human (cadaver) knees, after division of the internal lateral ligament the anterior cruciate ligament was torn by acute abduction of the tibia on the femur with the knee and hip joints flexed and the pelvis fixed.

In each instance the cruciate ligament was torn close to its tibial attachment, and in 1 instance a portion of the tibial spine was also torn away.

COMMENT

These results are in keeping with the experimental findings of McMaster [8] relative to tendon and muscle ruptures. This author found that normal tendon did not rupture even when subjected to severe strain, but that the tendon insertion pulled away, the muscle tore in its belly or at its origin or fracture of the bony attachment at either end occurred.

Miltner [9] in his work on the experimental production of articular sprains in rabbits noted that when considerable force was employed, in addition to synovial, subsynovial and articular changes, there was microscopic evidence "of a tearing injury at the point of insertion of the ligaments into the bone. Small bits of bone had been torn loose and tended to grow in the new location."

In Pellegrini-Stieda [10] disease, a delayed calcification or ossification of the internal lateral ligament appears as a semilunar shadow on the roentgenogram several weeks after an injury to the knee. It is usually adjacent, but distinctly separate from the medial femorocondylar angle, although Finder [11] has observed the process in other parts of the internal lateral ligament. Regardless of the various theories of origin, the vulnerability of the internal lateral ligament near its femoral attachment is once more apparent. The absence, roentgenographically, of pathologic calcification or ossification in those rabbit specimens in which the internal lateral ligament had been traumatized (fig. 5) may be considered evidence against the metaplastic theory and in favor of the belief that the process in Pellegrini-Stieda disease represents either a true, detached fracture of a spicule of bone or a fractureless callus formation due to periosteal tear.

The lateral and cruciate ligaments, like tendons, are therefore weakest and most susceptible to trauma at their osseous attachments, and one may anticipate, in the presence of adequate injury, the occurrence

8. McMaster, P. E.: Tendon and Muscle Ruptures, J. Bone & Joint Surg. **15:** 705, 1933.

9. Miltner, L. J.; Hu, C. H., and Fang, H. C.: Experimental Joint Sprain: Pathologic Study, Arch. Surg. **35:**234 (Aug.) 1937.

10. Stieda, A.: Ueber eine typische Verletzung am unteren Femurende, Arch. f. klin. Chir. **85:**815, 1908.

11. Finder, J. G.: Calcification of the Tibial Collateral Ligament: A Report of Forty-Two Cases, J. A. M. A. **102:**1373 (April 28) 1934.

of tears of the ligaments at these sites or even actual fractures of the bony insertions themselves, e. g., paracondyloid fracture of the femur or tibia or fracture of the tibial spine.

CONCLUSIONS

Although the following conclusions are derived from a study of knee joints in rabbits and in human cadavers, their application to the living human being is substantiated by clinical experiences and observations.

1. In rabbits, tears of the internal lateral ligament of the knee joint repair regardless of the size of the defect and whether or not fixation is employed. Tears of the cruciate ligaments do not repair by such simple fixation, and the severed ends can be approximated surgically only in the early stages after injury. It is suggested, in the light of anatomic studies which have revealed the primary importance of the internal lateral ligament to the stability and function of the knee joint, that the satisfactory results obtained by conservative fixation in human patients with tears of the cruciate ligament are due in reality to repair of associated injuries to the collateral ligament.

2. The ligaments of the knee joint in human cadavers and in freshly killed rabbits are weakest at or near their bony attachments, and these sites, in the presence of adequate trauma, are liable to varying degrees of tear or fracture.

RESULTS OF TREATMENT OF CHRONIC INDOLENT WOUNDS WITH AZOCHLORAMID

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BALTIMORE

Wounds involving the skin and the subcutaneous tissues are readily attacked by pyogenic organisms. In the majority of cases the superficial nature of the wound, which permits adequate drainage, results in satisfactory healing. A certain percentage of such wounds, however, become chronically infected because of some complicating factor, such as diabetes, a circulatory disturbance or trauma resulting in devitalization of the surrounding tissues. The protracted course of infected wounds in diabetic patients despite adequate diabetic therapy, the tenacious infections in wounds following the excision of carbuncles and the chronic sloughing wounds following subcutaneous trauma often discourage both patients and surgeons. The use of compresses wet with hot saline solution is beneficial in such cases, but the method is laborious and sometimes fails to clean up the infection. The present study was undertaken to determine whether a simpler and more effective method of treatment could be found, which would result in reducing the time and effort required to promote primary healing or to prepare such a wound for secondary surgical closure or grafting.

My attention was attracted to azochloramid, a new complex chlorine compound which liberates small amounts of chlorine gradually over a long period. This is in contrast with the rapid liberation of chlorine from Dakin's solution, which requires frequent changes of dressing and precautions against irritation.

In the present series of cases a stable oily solution, azochloramid in triacetin (1:500) was used in the following manner: Sterile sponges were soaked in this solution and applied directly to the wound. The saturated sponge was overlaid by a pad of abdominal gauze, and a sheet of rubberized silk or other impervious material was placed over this. Retention of the oily azochloramid solution on the wound surface was thus insured, and the dressing separated easily from the tender granulations. The dressings were changed twice daily by the nurse, who used a technic similar to that employed with hot sterile saline compresses. In the presence of spreading infections for which heat also is indicated, hot

sterile saline compresses are placed over the azochloramid sponges and the sheet of rubberized silk placed over the compresses.

While azochloramid may be of value as a dressing for several types of cutaneous wounds, it seems of special value in the treatment of large necrotic lesions. The best results have been obtained in cleaning up large granulating wounds and promoting growth of healthy granulation tissue either for secondary closure or for skin grafting. It is important to emphasize that this antiseptic does not take the place of careful surgical procedures and hot saline compresses when heat is indicated, as for an acute infection which is not localized.

In several cases of chronic infection which did not respond satisfactorily to other therapy, the application of azochloramid rapidly brought about improvement and shortened the time necessary before skin grafting or secondary closure.

The cases to be reported have been divided into three groups. Group 1 consists of 3 cases of chronic infection which did not respond satisfactorily to other forms of therapy; group 2 consists of 3 cases in which large, necrotic granulating wounds remained after excision of carbuncles, and group 3 consists of 2 cases of severe cutaneous flesh wounds with subsequent necrosis of the skin and superficial muscles in children. All of the cases have been followed carefully in the hospital, with pictures, cultures and frequent examinations to note the course.

GROUP 1

Case 1.—A white man aged 58, of Italian descent, was admitted to the hospital on Feb. 17, 1938, with varicose veins and a large, foul ulcer of the leg. He had been coming to this hospital for fourteen years because of a chronic ulcer of the left leg. Ligations and injections of numerous veins and various types of dressings had been employed during this period, but the ulcer had persisted and had become larger. The patient had persistently refused to cooperate by keeping off his feet and had once refused admission to the City Hospital after all arrangements had been made. On the present admission he did not appear ill, but a large, very foul ulceration covered a large area of the lower part of the left leg, from the ankle to the knee, on the anterior and medial aspects. The edges of the ulcer were rolled up and bluish. The surrounding skin was scarred and brown. The ankle and foot distal to the ulcer showed a thickened scar encircling the ankle. There was considerable peripheral edema. Proximally there were fairly extensive varicose veins, with a few smaller ones on the right leg (fig. 1).

The patient was kept in bed with the leg elevated. Hot sterile saline compresses, changed regularly (every two hours by day and every four hours by night), were applied to the ulceration. Roentgenograms revealed some evidence of osteomyelitis and extensive periostitis of the tibia and fibula of the left leg. The nonprotein nitrogen content and the sugar content of the blood were normal. There was little response to this therapy, the wound remaining necrotic, with poor granulations. The odor was so foul that the patient was isolated in a private room. A 1:500 solution of azochloramid in triacetin was then applied four times a day, soaked in
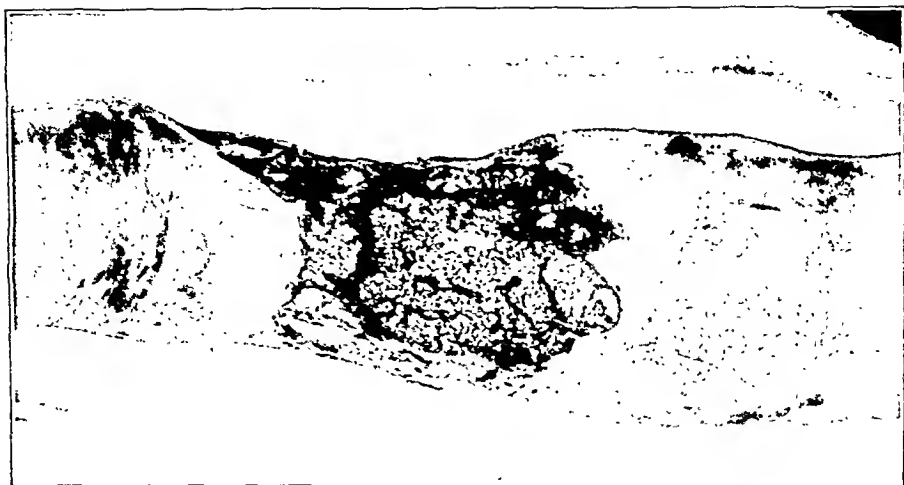
Fig. 1.—Indolent ulcer of the leg of many years' duration in a white man aged 58. He had had varicose veins for fourteen years. The Wassermann reaction was negative. Note the necrotic granulation tissue and the edema of the surrounding skin.
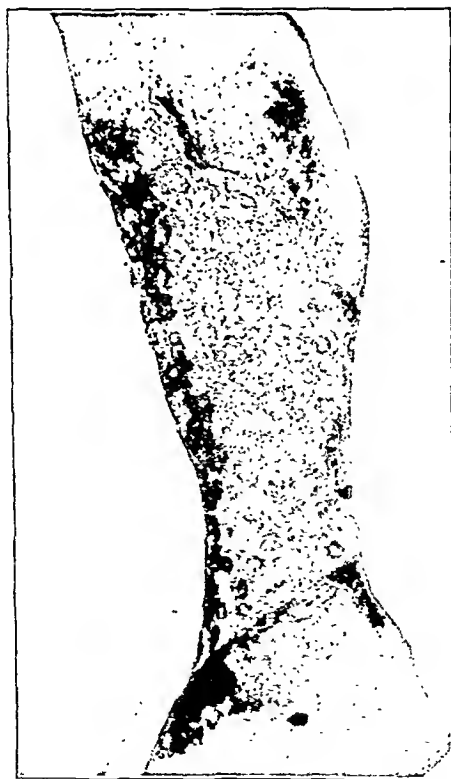
Fig. 2.—Same wound as in figure 1, twenty-four days later, after débridement and skin grafting.

sterile sponges. Within three days the odor had practically disappeared, and the granulations were cleaner. Within a week there was improvement in the cleanliness of the wound, although there was no regeneration of epithelium. In twelve days the cultures, which had shown a heavy growth of Bacillus proteus before azochloramid therapy was started, were sterile. The use of azochloramid was continued over a total period of twenty-one days. During this time the entire ulceration (15 by 15 cm.) acquired red, healthy granulation tissue, but there was little epithelization. The surrounding indolent skin was then debrided, and hot sterile saline compresses were applied for several days, after which a series of pinch grafts were applied at several subsequent operations, the majority of the grafts "taking" nicely (fig. 2).
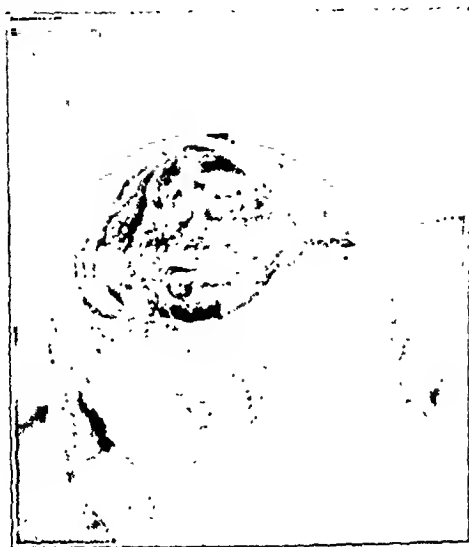
Fig. 3.—Infected amputation wound of the left thigh in a 72 year old white woman with diabetes, arteriosclerosis and gangrene of the left foot. Little response was shown to daily washing with alcohol, to dry dressings or to adhesive traction.

Case 2.—A 72 year old white woman had had diabetes for fifteen years. She was admitted to the hospital on Feb. 22, 1937, because of gangrene of the left great toe of six months' duration. The Wassermann reaction was negative. Despite all conservative measures there was no improvement in the gangrene, which progressed slowly and produced more pain. A Gritti-Stokes amputation at the knee was performed. Healing was satisfactory for one week, but infection of the stump developed, and on the tenth postoperative day the wound broke open, with wide gaping of the edges of the skin. There was no response to the use of alcohol and daily dressings with adhesive skin traction. Azochloramid in triacetin (1:500) was started, and the dressings were changed twice daily. Healthy granulation tissue soon developed, and after thirteen days the wound was clean. A secondary closure was then successfully performed (fig. 3).

Case 3.—A white woman aged 41 was admitted to the hospital on March 2, 1938, because of a tremendous ventral hernia with ulceration of the overlying skin (fig. 4). The hernia had been present for seven years, starting as a small umbilical hernia and increasing rapidly in size since her eighth pregnancy, with

ulceration of the skin two months before the present admission. Hot saline compresses were applied to the ulcerations to clean them up before a hernia repair could be performed. There was little improvement in the ulcerations after one week of continuous treatment, so a 1 : 500 solution of azochloramid in triacetin was tried. There was prompt improvement in the chronic ulcerations, which decreased in diameter from 2 to 3 cm. to 1 cm. during the eight days in which azochloramid was applied. The ulcerations were exposed to the air after the azochloramid was discontinued, and scarlet red was applied to stimulate epithelial growth. The ulcerations were completely healed at the end of ten days. Herniorrhaphy was then successfully performed, the wound healing by first intention.

Fig. 4.—Large ventral hernia with ulcerations of the skin in a 41 year old white woman. The ulcerations did not respond to hot sterile compresses.

GROUP 2

CASE 1.—A white man aged 59 was admitted to the hospital April 15, 1937. He was acutely ill, with signs of severe diabetes and a large carbuncle with a surrounding area of cellulitis involving the left shoulder. The sugar content of the blood on admission was 393 mg. per hundred cubic centimeters, and a test for acetone in the urine gave a 4 plus reaction. The Wassermann reaction was negative. Culture of the blood yielded bacteria, numerous colonies of Staphylococcus aureus being obtained. The patient received active treatment for the diabetes and septicemia. The shoulder was compressed with hot saline compresses for five days, after which the carbuncle was excised (fig. 5). Cultures revealed Staph. aureus from the carbuncle. Azochloramid in triacetin (1 : 500) was applied to the crater twice daily, hot sterile saline compresses being applied over the azochloramid sponges. The wound at the onset of treatment was dirty and necrotic, but despite the stormy course (five cultures of the blood yielded staphylococci) the wound began to show healthy granulation tissue. The surrounding cellulitis subsided, and after twenty-five days of treatment with azochloramid secondary closure of the wound was successfully done. During this time frequent cultures were made of material from the wound, which showed progressive diminution in the number of colonies of Staph. aureus.

Fig. 5.—Necrotic wound after excision of a carbuncle of the left shoulder in a 59 year old white man who was acutely ill with staphylococcic septicemia and severe diabetes.
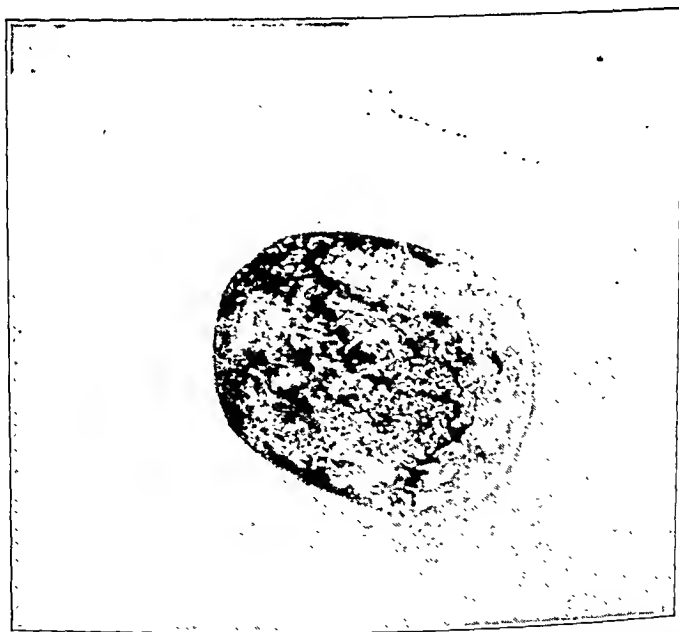
Fig. 6.—Condition in a white woman aged 52, with diabetes, after excision of a carbuncle of the right interscapular region. Note crusting and unhealthy appearance of the base of the wound after eight days' treatment with hot sterile saline compresses.

Case 2.—A white woman aged 52 was admitted to the hospital March 31, 1937, with a diagnosis of diabetes mellitus and a large carbuncle on her back. The diabetes was easily controlled, and hot saline compresses were applied to the carbuncle. After eight days the carbuncle was thought to be sufficiently localized for excision. This was done successfully, Staph. aureus being cultured from the wound. The crater was 7 cm. in diameter (fig. 6). Healing was delayed, and after eight days azochloramid in triacetin (1:500) was tried in an endeavor to speed up the healing of the wound. After four days of therapy with azochloramid and hot sterile saline compresses there was a marked improvement in the appearance of the wound. Red granulation tissue grew rapidly, decreasing the depth of the crater. Fourteen days after the azochloramid treatments were begun the wound was grafted with small pinch grafts, which "took" satisfactorily.

Fig. 7.—Large deep wound after excision of a carbuncle of the neck in a 54 year old white man. Spreading of this wound occurred, so that a second incision was necessary. Azochloramid was subsequently discontinued.

Case 3.—A white man aged 54 was admitted to the hospital March 5, 1938, with a large carbuncle on the back of his neck, of two weeks' duration. The carbuncle was compressed for two days before surgical excision was performed (fig. 7). Cultures revealed Staph. aureus. Azochloramid in triacetin (1:500) was applied on the second day after the operation. Hot sterile saline compresses were applied over the azochloramid sponges. The wound did not respond satisfactorily, for the carbuncle spread to the opposite side of the neck. Accordingly, a second excision of the area of spread was necessary one week later. The diameter of the crater was now 9 cm. and its depth 1.5 cm. Azochloramid was again applied, but after two days the patient complained of such pain and irrita-

tion of the wound when it was applied that the azochloramid was discontinued. At the time of writing the wound is healing slowly with hot sterile saline compresses.

<div align="center">GROUP 3</div>

CASE 1.—A white boy aged 1½ years caught his left arm in a washing machine wringer, traumatizing the subcutaneous tissues. The skin and bones were not

Fig. 8.—Sloughing wound of the left forearm of a 1½ year old child whose arm was caught in a washing machine wringer. Note the surrounding inflammation of the skin.

Fig. 9.—Wound similar to that in figure 8 in a 3½ year old Negro boy. There was also a surrounding area of induration and inflammation, which caused this wound to respond better to hot sterile saline compresses than to azochloramid.

injured. The boy was admitted to the hospital for observation on Feb. 19, 1938, and several days later the subcutaneous tissues and skin in the anticubital fossa began to slough. A foul, necrotic sloughing area about 5 cm. in diameter developed

(fig. 8). Culture revealed an alpha streptococcus. Azochloramid in triacetin (1:500) was applied on gauze sponges twice a day. The wound began to look more healthy, but repair was sluggish. After eight days, treatment with azochloramid was discontinued, and the use of hot sterile saline compresses was instituted, with slightly more rapid improvement. Grafts were applied to the area about a week later, but only approximately half of them "took"; hence secondary closure was necessary ten days later.

CASE 2.—A Negro boy aged 3½ years was admitted to the hospital on March 2, 1938, for observation, with an injury similar to that in the foregoing case. He had caught his arm in a washing machine wringer, injuring the soft parts but not the bone. While he was in the ward, an area about 5 cm. in diameter over the brachioradialis muscle began to slough. Application of hot sterile saline compresses were begun, but after two days it was discontinued and azochloramid in triacetin (1:500) started. The repair of the wound was slow, and after eight days' treatment the azochloramid was discontinued and the use of hot sterile saline compresses again started. The improvement under the latter therapy the second time was definite, which illustrates the point that azochloramid will not act as a substitute for local heat in the treatment of wound infections which are not sufficiently localized (fig. 9).

SUMMARY

Eight large, necrotic infected wounds have been treated with azochloramid in triacetin (1:500). The wounds selected have been indolent in character, most of them complicated by other factors, such as diabetes or vascular disease. Six of the 8 presented localized infection, 2 infections being in a less localized stage.

A satisfactory response was obtained in 5 of the 6 cases. The character of the granulation tissue changed after a few days from sluggish, gray granulations into a rapidly growing bed of red granulation tissue of healthy appearance.

In the sixth case there were signs of irritation on the second day, and the solution was discontinued.

In the other 2 cases the infections were not sufficiently localized, and hot saline compresses seemed of greater value.

In conclusion, it may be stated that azochloramid (1:500 solution in triacetin) is an antiseptic which appears to be of value in the treatment of chronic infections of the indolent type described. Sterile sponges soaked in this solution, changed twice or four times daily, exert a continuous antiseptic action and require a minimum of attention. The solution promoted development of healthy granulation tissue, or primary healing, in a group of infected wounds for which other types of therapy previously tried had offered little or no benefit.

SIXTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Madelung's Deformity.—Anton and his associates [1] review 171 cases of Madelung's deformity collected from the literature and add 1 case of their own. They find that this deformity may involve any or all of the structures about the wrist. It is essentially, however, a defect of the lower end of the radius, an osteochondritic dysplasia with palmar bowing of the distal end of the radius. Posterior subluxation of the lower end of the ulna, always present, is more apparent than real. In the more severe forms there may be overriding of the ulna on the carpal bones. In 127 of the 171 cases reviewed, the deformity was bilateral. Heredity seemed to play a part in the development of the lesion in one third of the cases. The patients commonly had pain during the growing years, which ceased when growth in the radius ended. The authors advise palliative treatment until growth is attained, after which the most satisfactory treatment, they believe, is osteotomy of the lower end of the radius with correction of the bowing and shortening of the ulna if necessary.

This report of progress is based on a review of 198 articles selected from 334 relating to orthopedic surgery and appearing in the medical literature approximately between July 1 and Nov. 1, 1938.

1. Anton, J. I.; Reitz, G. B., and Spiegel, M. B.: *Ann. Surg.* **108**:411, 1938.

Congenital Anomalies of the Spine.—Bailey and Carter [2] in a study of spinal anomalies attempt to correlate the anatomic, roentgenologic and clinical findings. They find that anomalies occur in 67 per cent of spines. They discuss the development of fused vertebrae, hemivertebra, spina bifida, transitional vertebrae, spondylolisthesis and persistent epiphysis of the vertebral process. The latter anomaly is sometimes of medicolegal importance. It can be differentiated from a fracture by the following observations: 1. The epiphysis is separated from the other portion of the vertebra by cartilage. 2. There is absence of compression of the vertebral body. 3. There is no offset of the fragment. 4. It does not change place with motions of the spine.

Early Treatment of Congenital Dislocation of the Hip.—Emphasizing the necessity for early diagnosis and treatment of congenital dislocation of the hip, Kickehayn [3] reviews the material collected between 1930 and 1935 at three large German clinics. During this period 39 dislocations were reduced during the first year of life, 117 in the second and 56 in the third. There was no recurrence of dislocation in the first year group; there were 6.8 per cent recurrences in the second year group and 7.1 per cent in the third year group. Often the oblique acetabular roof of the dislocated hip became a normal roof. This observation was frequent in cases of dislocation reduced during the first year. Rapid acetabular development was also shown during treatment in the preluxated type. In the cases reported the children were fitted with abduction splints after approximately seven weeks in plaster. The author feels that in the preluxation stage the abduction treatment offers at present the best prospects. The available statistics are scanty and for the most part are too recent to permit of any assurance. He cites a fifteen year follow-up by Elsner on a hip reduced at 5 months. The result was faultless.

Aberle [4] reports 4 cases of hallux varus of congenital origin, adding them to the 70 cases already reported in the literature. This deformity of the first metatarsal bone and phalanges is characterized also by marked broadening of the component bones of the first toe. This broadening is a consequence of congenital duplication of the "big toe ray." All variations, from separate to fused duplicate bones, have been reported. One patient presented, in addition to congenital varus, unusual shortening and broadening of the tibias as well as bilateral congenital dislocation of the fibulas at the knees. Correction is often necessary to permit the wearing of a shoe. The author prefers to resect the base of the proximal phalanx or to combine this resection with resection of the head of the first meta-

2. Bailey, W., and Carter, R. A.: California & West. Med. **49**:46, 1938.

3. Kickehayn, R.: Ztschr. f. Orthop. **67**:245, 1938.

4. Aberle, W.: Ztschr. f. Orthop. **67**:165, 1938.

tarsal bone. This gives adequate relaxation of the contracted phalanx. He advises that incisions be placed laterally rather than medially.

DEVELOPMENTAL DISEASES OF BONE

Coxa Plana Following Severe Trauma.—Nielson [5] reports 2 cases of coxa plana subsequent to fracture of the neck of the femur, in boys. He postulates an injury to the nerves of the afferent blood vessels. The resultant impairment of nutrition leads to osseous and cartilaginous changes. In the opinion of the author, the severity of the lesion is dependent on the degree of impairment of the circulation.

First Stages of Coxa Plana.—Waldenstrom [6] states that in the very earliest stage of coxa plana the change shown in the anatomic specimen is primary necrosis followed by resorption of the necrotic cancellous tissue and later by formation of new bone and cartilage. Of the patients who have been personally treated by him during the past thirty years, 13 came under his observation at this early stage of the disease. The first symptom of the disease was a limp, sometimes associated with pain in the hip. Also, there was restriction of mobility which when compared with that of the sound hip could be expressed in degrees. Four patients consulted the author when limping had been present for only a few weeks. An anteroposterior roentgenogram taken at that time was normal. Unfortunately, a lateral view was not taken. The author feels that a lateral view always shows the deformity more definitely. Two or three months after the start of limping the characteristic signs of coxa plana appeared; i. e., the normal cancellous tissue in the upper part of the epiphysis began to show on the articular surfaces the effects of resorption. The roentgenograms in these cases of incipient coxa plana showed one constant change in the diseased hip joint, an increase in the distance between the epiphysis and the bottom of the acetabulum. The article is well illustrated by roentgenograms.

TUBERCULOSIS

Fusion of the Spine.—Swift [7] tabulates the end results of the fusion operation for tuberculosis of the spine in 309 children 10 years old or younger. All of these children were operated on at the New York Orthopaedic Dispensary and Hospital between 1911 and 1932. Seventy-four per cent were found to be leading a normal life without recurrence of the disease. Fifteen per cent had pseudarthroses which required further operations. In 11 per cent the results were poor. Fifteen per cent of the children have died. Two children died of the operation.

5. Nielson, B.: Hospitalstid. **81:**773, 1938.

6. Waldenstrom, H.: J. Bone & Joint Surg. **20:**559, 1938.

7. Swift, W. E.: J. Pediat. **13:**248, 1938.

POLIOMYELITIS

Studies of Poliomyelitis.—Brodie [5] states that neither the portal of entry nor the pathogenesis of poliomyelitis has been finally determined in the human being. Therefore too close an analogy between the experimental and the human disease cannot be drawn. He concludes that there is evidence that more than one strain of virus exists. Neither convalescent serum nor any of the other means of treatment available offers hope for the prevention or limitation of paralysis. The value of active immunity as a preventive is still undetermined. Nasal sprays are effective in protecting monkeys, but in human beings the results from the use of these sprays are not encouraging.

OSTEOMYELITIS

Subacute Infection of Bone.—Kuth [9] reports 4 cases of subacute infection of bone. or osteoperiostitis albuminosa Ollier, and gives an excellent review of the subject. This infection is caused by a pathogenic organism of low virulence. The lesions are mild and benign and respond to simple incision with adequate drainage and removal of sequestrums. The article is well illustrated.

CHRONIC ARTHRITIS

Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D.—Abrams and Bauer [10] observed the effects of massive doses of vitamin D on 18 patients with rheumatoid arthritis over periods of from four to thirteen months. Prior to treatment all the patients were in a state of stationary or slowly progressive illness. Subjective improvement was observed during treatment in 8 patients. In only 3 patients was objective improvement observed and in only 1 was it marked. Other observations were equally disappointing. The conclusion was that massive doses of vitamin D are of little value in altering the course of the disease. The effects of the large doses did not differ from those of the usual therapeutic doses and did not justify the expense and danger involved.

Osteoarthritis Cretinosa.—Ludwig [11] suggests that the changes found in the bones and joints of cretins be named "osteoarthritis cretinosa." In only 2 of 49 adult cretins were the hips normal in roentgenologic examination. The abnormalities noted were flattening and broadening of the

8. Brodie, M.: Am. J. Pub. Health **28**:746, 1938.

9. Kuth, J. R.: Subacute Infections of Bone: Osteoperiostitis Albuminosa Ollier, Arch. Surg. **37**:46 (July) 1938.

10. Abrams, N. R., and Bauer, W.: The Treatment of Rheumatoid Arthritis with Large Doses of Vitamin D, J. A. M. A. **111**:1632 (Oct. 29) 1938.

11. Ludwig, H.: Fortschr. a. d. Geb. d. Röntgenstrahlen **57**:506, 1938.

femoral head, shortening of the neck, enlargement of the trochanters and irregular calcification. When the process was advanced there were arthritic changes, including free joint bodies. In the hips of children, irregularity in ossification was found. The picture simulated Legg-Perthes disease.

[Editorial Note.—One of the editors has observed roentgenograms of cretins which show a picture similar to that of coxa plana. In cretins this condition is always bilateral.]

Postural Education.—Posture: Malcolmson [12] reviews the experience of the United States Naval Academy in postural training since 1921, when such training was introduced as a part of the physical examination of cadets. He gives five rules for postural training: 1. Stand with the heels together and the toes at an angle of 45 degrees. 2. Contract the buttocks slightly. 3. Clasp the forefingers lightly together behind the buttocks. 4. Raise the chest. 5. Release the hands and let gravity determine their position. Special instruction is given for the correction of local defects as shown in silhouette pictures. Malcolmson states that postural training should be started in early childhood; in this way many structural lesions would be prevented. He deplores the lack of agreement in definitions of good posture and feels that a generally acceptable concept would be reached if there were more studies of posture.

[Editorial Note.—While there is lack of unanimity in defining good posture, there is fairly general agreement as to the end to be attained—a physically efficient body. There is, however, wide disagreement as to methods, which vary from supine relaxation to strenuous and rigid exercises. No method brings rapid correction. Probably with more attention to the carriage of the body in early childhood the tedious correction of faulty posture at a later age would not be necessary.]

BACK

Treatment of Scoliosis by Osseous Traction.—Goodwin and Althaus [13] make a preliminary report on traction applied directly on the spine for the correction of scoliosis. This was carried out in 2 cases after moderate correction had been obtained with the Risser jacket. Immediately after an operation for spinal fusion had been performed, stainless steel wires were applied about the spinous processes of the vertebrae in the compensatory curves and were then threaded under the muscles to the side of the body. The wires were made taut over a nail on the outside of the plaster cast. The wires were well tolerated, and much additional correction was obtained. In neither of the cases has

12. Malcolmson, J. E.: Arch. Phys. Therapy **19:** 348, 1938.
13. Goodwin, F., and Althaus, J. W.: Southwest. Med. **22:**253, 1938.

sufficient time elapsed to permit one to see whether the added correction will be permanent.

Treatment of Scoliosis by Means of the Wedging Jacket and Spinal Fusion.—Two hundred and sixty-five cases of scoliosis treated by the use of a wedging jacket and spinal fusion are reported by Smith, Butte and Ferguson.[14] In the eight year period covered by this study, 1,498 new cases of scoliosis were observed in the clinic of the New York Orthopaedic Dispensary and Hospital. In only 297, or 19 per cent, was operation performed. The indications for correction and fusion are: (1) a curve which is progressing in a growing child; (2) a severe curve with imbalance of the trunk, whether or not the patient is beyond the period of growth and (3) a deformity which is causing pain or fatigue. In some of the cases reported an operation was performed without previous correction. Some of the patients were given postural treatment. Three of these showed measurable improvement after corrective exercises. The jacket used is essentially the same as that first used by Risser in 1927 and described by him in 1931, the only modification being that the head is held in position toward the side of the concavity of the curve, to prevent undue stretching of the brachial plexus. This position, however, is not held forcibly to produce correction, as was previously advocated. The hinges are now placed more eccentrically, toward the convexity of the curve. In addition to straightening the primary curve, the wedging jacket simultaneously increases the compensatory curve. This change in the secondary curve is observed only while the patient is in the jacket. After the jacket is removed, the compensatory curve should straighten in proportion to the straightening obtained in the primary curve. The primary curve is determined by the criteria described by Ferguson: 1. In the case of three curves, the middle one usually is the primary curve. 2. The greater curve, or the one toward which the trunk is shifted, usually is the primary curve. 3. When in the sitting position the pelvis is elevated on the side of the convexity of the lumbar curve; this curve if it is compensatory will tend to straighten but if it is primary it will not. The operation is performed with the patient in the jacket. If the primary curve has been straightened completely, the fusion is limited to the vertebrae included in it. It is important that the end vertebrae should not be overcorrected; this may occur in a mild flexible curve. When correction is not complete, it may be advisable to extend the fusion beyond the limits of the primary curve. The object should be to extend the fusion to the part where the upper surface of the upper vertebra will be parallel to the lower surface of the lower vertebra. These surfaces should be at right angles to a line joining their centers. The time required for correction of the curve, including the application

14. Smith, A. DeF.; Butte, F. L., and Ferguson, A. B.: J. Bone & Joint Surg. **20**:825, 1938.

of the jacket and preparation for the operation, is from three to four weeks. Hibb's method of fusion is used in all cases. If four or more vertebrae are included in the fusion, the operation is done in two or more stages. This minimizes the occurrence of shock. The patient remains in the original jacket for three months after the last operation and during this time is kept in bed. The jacket is then removed, and a so-called semibent jacket is applied. It is put on with the patient lying supine on a strip of canvas. No attempt is made to straighten the back more than occurs naturally. A strip of plaster is included over the shoulder opposite the curve in order to hold the head and neck. The patient is now permitted to be up. At the end of three months the jacket is again changed and the shoulder strap is omitted. When this jacket is put on, the spine usually has nearly, but not completely, become straight. This jacket is removed in three months, and a roentgenogram is taken. If the fusion is continuous and mature, no other plaster is applied. . No jacket, therefore, remains on longer than nine months unless the size of the patient or the appearance of the fusion in the roentgenogram makes it necessary to alter this rule. Pseudarthrosis occurred in the area of fusion in 61, or 23 per cent, of the 265 patients. Forty-seven of these patients were operated on again and the defect repaired. This pseudarthrosis occurred in the thoracolumbar region in 36 of the 61 cases. This indicates that particular care should be taken to produce strong fusion in this area. The results of the treatment were excellent or good in 79.7 per cent, fair in 15.6 per cent and poor in 4.7 per cent of cases.

[EDITORIAL NOTE.—Scoliosis remains one of the most difficult problems in orthopedic surgery. Admitted that the ideal treatment would be the prevention of scoliosis for the most part by corrective exercises for early muscular imbalance and the use of minimal supportive apparatus to maintain normal spinal contour, most patients seek treatment when such preventive measures are no longer possible. The careful work of this clinic has added greatly to knowledge of the mechanics and treatment of scoliosis.]

MUSCULAR DISTURBANCES

Isolated Paralysis of the Serratus Anterior Muscle.—So-called winged scapulas attributable to paralysis of the serratus anterior muscle were first described in 1825 by Velpeau. Since that time 150 cases have been reported, in most of which the condition was considered to be due to injury or disease of the long thoracic nerve rather than to laceration of the muscle itself. Horwitz and Tocantins[15] report 6 cases. The pathogenesis and kinesiologic observations are considered. Treatment

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15. Horwitz, M., and Tocantins, L. M.: J. Bone & Joint Surg. **20**:720, 1938.

consists in relaxation of the paralyzed serratus anterior muscle and correction of the associated stretched and contracted muscles. The authors claim that this is effectively performed by a brace which they have illustrated. This brace eliminates both the winging and the abnormal rotation of the scapula. The authors recommend this apparatus also for the treatment of neuritis of the brachial plexus as well as cervical rib or scalenus anterior syndrome. The brace consists of a celluloid elbow, or cup, into which the point of the elbow fits snugly. It is held in place by an adjustable steel upright which rests on a chest band, a pelvic band and an iliac crest seat.

Scalenus Anterior Muscle in Relation to Pain in the Arm and Shoulder.—In addition to the scalenus anterior syndrome, which Ochsner and his associates [16] describe as characterized by pain referred to the shoulder, to the supraclavicular area, down the arm to the ulnar and flexor surfaces of the forearm, to the hand and frequently to the side of the neck and ear, Freiberg [17] finds that the pain is also present in an area between the spine and the mesial border of the scapula. Also, if the head is turned toward the affected side with the neck extended, on deep inspiration or on depression of the shoulder the pain is increased. The vascular manifestations consist of diminished pulse volume on the affected side, decreased temperature of the cutaneous surface, dulness, coldness and formication. These vascular changes can be proved by oscillometric tests. In cases in which the sternal end of the shoulder girdle presents arrested descent or in which the acromioclavicular descent is increased, symptoms develop. The author points out that lesions of the cervical portion of the spine as well as traumatic and infectious lesions of the shoulder girdle may be accompanied by the scalenus anterior syndrome but that section of the scalenus anterior muscle may not be necessary. When cervical lesions or lesions of the shoulder girdle are amenable to conservative therapy, such as improvement of general posture, rest in bed, traction on the forearm and upper part of the arm and wearing of braces, indiscriminate scaleniotomy is contraindicated. On the other hand, when there is anatomic malformation or when symptoms have been present a long time, with hypertrophy or contracture of the scalenus anterior muscle, scaleniotomy is indicated.

Treatment of Cerebral Palsies.—Phelps [18] stresses the complicated nature of the treatment required for cerebral palsy. The program must start in infancy and be correlated by the pediatrician, the orthopedist, the neurologist and the physical therapist. Educational and often

16. Ochsner, A.; Gage, M., and DeBakey. M.: Am. J. Surg. **28:**669, 1935.

17. Freiberg, J. A.: J. Bone & Joint Surg. **20:**860, 1938.

18. Phelps, W. M.: Care and Treatment of Cerebral Palsies, J. A. M. A. **111:** 1 (July 2) 1938.

psychologic aid are also needed. The general plan is to start in the primary stages with physical therapy and then to graduate into occupational therapy and finally into vocational training. Surgical intervention (when necessary) is considered only a step in the general treatment and is never curative in itself.

CIRCULATORY DISTURBANCES OF THE EXTREMITIES

Erythermalgia.—Smith and Allen [19] report the cases of 5 patients suffering from erythermalgia. They consider this a better name than the one given to the condition by S. Weir Mitchell, erythromelalgia. There is increased sensitiveness of the skin to rise in temperature above a certain point. The skin becomes red, hot and painful. One or more extremities may be involved. The condition may be primary, or it may be secondary to polycythemia. At present the treatment of choice is uncertain. A rise in cutaneous temperature above the critical point should be avoided if possible. Desensitization with baths of gradually increasing temperature may be tried. Roentgen therapy may sometimes be helpful.

Intermittent Vascular Occlusion in Peripheral Vascular Disease.—Collins and his co-workers [20] state that improved circulation in peripheral vascular disease is dependent on release of vasospasm and improvement of the collateral circulation. They report on 137 cases in which a pneumatic cuff was used about the thigh to produce intermittent venous compression. In the presence of open lesions, pressures of 30 to 40 mm. of mercury were used. When no lesions were present, pressures of 60 to 80 mm. were used. There were alternate periods of compression for one minute and release of compression for two minutes. There was prompt relief of pain in most instances, with healing of the ulcers in over 60 per cent. The diseases for which this treatment was tried included thromboangiitis, arteriosclerosis (diabetic and senile) and acute thromboses.

Peripheral Arterial Disease.—Samuels [21] divides peripheral arterial disease into two types: (1) organic disease and (2) vasomotor imbalance. He feels that palpation of the vessels of the foot is not a good way to determine circulatory efficiency. He has found the best clinical procedure to be that of watching the pallor of the sole of the foot with the leg raised 45 degrees from the supine position. While this is being done the patient rapidly flexes and extends the ankle. Differences

19. Smith, L. A., and Allen, E. V.: Am. Heart J. **16:**175, 1938.
20. Collins, W. S.; Wilensky, N. D., and Ginsberg, H.: Arch. Phys. Therapy **19:**261, 1938.
21. Samuels, S. S.: J. M. Soc. New Jersey **35:**224, 1938.

in cutaneous temperature, atrophy of the muscles of the calf and vascular calcification as observed roentgenographically are also useful criteria. In the presence of disease, smoking should be forbidden, and the natural heat of the extremity should be preserved with warm clothing. Hot baths and diathermy may be used to warm the limbs. Local means of applying heat should not be used. e. g., hot water bottles, which frequently cause burns. Intravenous injection of 300 cc. of a 2 per cent solution of sodium chloride every other day is helpful. This should not be used if there is nephritis or myocarditis. Exercises for the limb may be given if there are no lesions. The use of suction and pressure apparatus has not given particularly good results in organic lesions.

FOOT

Form of Foot of Mountain Nomads.—Frinak [22] made a study of the feet of the mountain nomads of Anatolia, who clamber over rocks continually. For shoes they wear a piece of hide tied on with thongs. The author examined 40 males and found them to possess uniform and characteristic feet. The form of the foot is grossly normal in that there is no flat foot and no valgus at the ankle. The foot is extraordinarily broad, measuring 11 to 13 cm. at the base of the toes. This width diminishes at the middle of the foot to 6 or 8 cm. The great toe uniformly deviates laterally from 12 to 16 degrees. The musculature of the toes and feet is unusually well developed. The great toe can be flexed 40 degrees dorsally and 70 degrees plantarward.

Roentgen Treatment of Plantar Warts.—Popp and Olds [23] report the results of roentgen treatment in 91 cases of plantar warts. In this series. 58 patients, or 63 per cent, were cured, whereas 18 patients, or 19 per cent, received no benefit whatever. In 40 of the 58 cured patients the lesion or lesions disappeared after one treatment : 11 required two treatments ; 5 required three. and 2 were cured after four treatments. Thirty-two patients reported increased tenderness of the lesion in from seven to ten days after treatment. The average interval between the beginning of treatment and the disappearance of the lesions was six weeks.

[EDITORIAL NOTE.—Apparently several types of plantar warts are found. Some disappear spontaneously ; others recede when undue pressure on certain areas of the foot is relieved by proper shoes or supports. Still others seem to be associated with epidermomycoses and to disappear with treatment of the fungus infection. Roentgen therapy is an effective treatment for many of them.]

22. Frinak, S.: Ztschr. f. Orthop. **67**:396, 1938.
23. Popp, W. C., and Olds, J. W.: Radiology **31**:218, 1938.

OSSEOUS TUMORS

Giant Cell Tumor of Bone.—Coley and Higinbotham [24] state that the cause of this tumor remains unknown but that the traumatic theory offers the most logical explanation. The giant cell tumor of bone is found most frequently at the distal end of the femur and at the proximal end of the tibia, near the epiphysial line. The radius, humerus, ulna and fibula, in the order named, are the next most frequent locations. The giant cell tumor is usually benign, but occasionally it is encountered in a malignant form and this may represent a transformation of a tumor which was histologically benign at the onset. Treatment rarely consists in amputation. Surgical extirpation is preferable for accessible tumors and irradiation for inaccessible or extremely advanced growths. Caution should be exercised in using the roentgen ray, and histologic confirmation of the diagnosis should be secured in cases in which there may be an osteolytic sarcoma, which bears a close resemblance roentgenologically to the giant cell tumor. Irradiation should not be used in conjunction with surgical treatment; either the surgical method should bear the full responsibility or irradiation should. One must remember that the roentgen ray in large doses destroys the regenerative powers of bone. In small doses it may fail to arrest the disease; therefore, the exact dosage for the individual case is still a matter which no one understands. Still, inexpert irradiation is probably less hazardous than operation in the hands of one not familiar with surgical operative details, though loss of limb may ultimately result in either instance. If one resorts to operation, removal of all the tumor tissue through adequate exposure, careful closure of the wound without packing or drainage and primary healing of the wound should be sought. Of course, when surgical extirpation results in a weakening of the bony structure, protection during the regenerative phase is essential, for a pathologic fracture may cause functional impairment, and a painful condition of the neighboring joint may result.

Dawson and his associates [25] conclude that giant cell tumor of bone is a neoplastic growth probably originating with trauma and hemorrhage and developing as an osteogenic tissue reaction and proliferation which may slowly progress and ultimately regress but which in rare cases assumes the characteristics of an osteogenic sarcoma. It may be classed as a type of new growth intermediate between purely reactive tissue and true blastoma. Appended are 45 excellent photomicrographs of the types of tissue reaction met with, accompanied in each case by exceptionally lucid histologic and clinical notes.

24. Coley, B. M., and Higinbotham, N. L.: J. Bone & Joint Surg. **20:**870, 1938.
25. Dawson, E. K.; Innes, J. R. M., and Harvey, W. F.: Edinburgh M. J. **45:** 491, 1938.

Primary Hemangioma Involving Bones of the Extremities.—Primary hemangioma of bone is a relatively uncommon tumor. Although Topfer [26] collected 257 cases of nonsymptomatic primary hemangioma of bone during 2,154 autopsies, in only 3 instances were the lesions in the extremities. The vertebrae were involved in all cases, and there were 34 instances of multiple lesions. Geschickter and Maseritz [27] were able to find reported in the literature only 11 cases of symptomatic primary hemangioma involving bones of the extremities, and they have added 4 more cases. The ages of the patients varied between 8 and 20 years. The distribution in regard to sex was equal. Three of the 4 patients gave a history of trauma. The roentgenologic changes characteristic of primary hemangioma of bone in an extremity are similar to those associated with benign giant cell tumor or osteitis fibrosa cystica, but there may be several significant features. First, the lesion tends to progress and may be more extensive than the other lesions under consideration commonly are. Second, the locules, when present, are smaller than the locules of benign giant cell tumor or benign bone cyst and are bordered by a much heavier framework of osseous tissue. Primary hemangioma of bone gives rise to cystic cavities which contain no capsular lining. Like bone cysts, they may contain fluid or tumor tissue within the wall. The tumor tissue filling these cavities is apparently similar to the tissue of angiomatous tumors elsewhere. The microscopic characters are various, and in the author's series there were a capillary hemangioma, cavernous hemangioma, an angioblastma and an angiosarcoma. A section of the capillary hemangioma showed areas of hemorrhage between which could be seen capillaries with their single layers of endothelium and a hyalin content. The tissues contained large cystic cavernous spaces filled with red blood cells and an occasional lymphocyte or polymorphonuclear leukocyte. Thus far the most valuable method of treating primary hemangioma of bone has been irradiation. Complete cures have been reported in a number of instances. The value of curettement is questionable. Resection of bone has been reported in several cases and has proved to be a means of absolute cure. The angioblastoma of bone in the case reported is the first to be described in the literature.

Myositis Ossificans.—Clinical and pathologic data on 25 cases of myositis ossificans, including both the circumscribed and the progressive form, are reviewed by Geschickter and Maseritz.[28] The circumscribed form is divided into only two clinical varieties, traumatic and nontraumatic. Fifteen of the patients, or 60 per cent, gave a history of

26. Topfer, D.: Frankfurt. Ztschr. f. Path. **36**:337, 1938.

27. Geschickter, C. F., and Maseritz, I. H.: J. Bone & Joint Surg. **20**: 888, 1938.

28. Geschickter, C. F., and Maseritz. I. H.: J. Bone & Joint Surg. **20**:661. 1938.

injury preceding muscular ossification. One case was noted in which there was fracture but no dislocation. The thigh was involved in 14 instances, the arm in 3, the elbow in 2 and the cervical and lumbar muscles in 1 instance each. The age of onset varied from 13 to 72 years. Sex appeared to be an outstanding factor: 23 patients were males. Two patients had myositis ossificans progressiva. Here trauma played an important role, but the etiologic agent is unknown. Both patients were females. The earliest physical finding is a viscid mass which gradually becomes indurated. It may make its appearance within a few hours. Roentgenograms at first show small discrete dense shadows which lie some distance from the normal bone. These areas gradually become confluent and form one large spicule of bone. The earliest roentgenographic appearance was nineteen days. The so-called dotted veil appearance has been called pathognomonic. When exposed at operation, the bone lesion is usually surrounded by a cartilaginous substance which appears to be the result of degeneration of muscle. Beneath this material a fibrous capsule is found. Radiating from the capsule are irregularly distributed bands of connective tissue which invade the bone. Occasionally cystic changes are found. The earliest histologic manifestations are degeneration of muscle, hyperplasia of connective tissue and organization of hemorrhage. There appears to be a tendency toward capsule formation, which is almost simultaneous with calcification of the inner portion of young connective tissue. Aggregations of colloid-like particles and bits of cartilage appear in some cases. Cartilage was distinguished in one fourth of the authors' cases. There was a single instance of malignant tumor complicating traumatic myositis ossificans. Conservative treatment is preferable. Postoperative recurrences are common in cases in which surgical removal is attempted before the condition has been present for six months or in which resection is not complete. Roentgen treatment is being tried; the results cannot be determined yet. Ossification occasionally regresses.

Osseous System in Hodgkin's Disease.—Abrams [29] made a study of 10 consecutive cases of Hodgkin's disease referred to the Brooklyn Cancer Institute. Two of the patients were found to be suffering from closely related diseases, lymphoepithelioma and lymphosarcoma. Of the remaining 8 patients, 6 showed involvement of the osseous system. The lesions are commonly multiple and may be osteoplastic, osteoclastic or both. The osseous lesions are usually demonstrated late in the course of the disease. Pain is commonly the first sign of osseous involvement. Roentgen therapy is palliative and retards the progress of the disease.

Skeletal Metastases in Cancer of the Breast.—There are three principal types of osseous localization for metastases from carcinoma of the

29. Abrams, H. S.: Ann. Surg. **108**:296, 1936.

breast.[30] Every large extension to the skeleton begins with a vertebral lesion, which extends later to the shoulder girdle and still later to the pelvic girdle. Finally, the entire skeleton may be involved if the patient survives. Involvement of a large part of the spine is more common than involvement of a single vertebra. There are three types of metastasis: (1) the osteolytic type, characterized by destruction and dissolution of bone; (2) the osteoplastic type, forming dense bone, and (3) the mixed type resembling Paget's disease, showing an osteolytic area surrounded by thickened cortex and sometimes presenting a mottled appearance. In general there are three distinct syndromes caused by metastases to bone from tumors of the breast: 1. The vertebral syndrome, or pseudo Pott's syndrome. The patient complains of pain in the spine, usually persistent day and night and not relieved by rest or immobilization. The symptoms tend to progress, fracture may occur, and compression of the spinal cord may result. 2. The scapulohumeral syndrome. The patient complains of pain in the shoulder, particularly in the region of the upper part of the humerus. Mild radiation of pain may occur but it is not like that of root pain. There is localized tenderness over the clavicle, the scapula or the humerus, with muscle spasm and weakness. The symptoms progress gradually and may result in a fracture, most commonly through the surgical neck of the humerus. 3. The pelvitrochanteric syndrome. The patient complains of pain in the hips, the pain being located in the region of the ilium, the pubis, the ischium or the greater trochanter. There may be vague radiation down the femoral or sciatic nerves. Spontaneous fractures through the upper part of the femur or in the pelvis may result. Any of these syndromes may progress until the metastases are spread diffusely throughout the skeleton.

Diagnosis of Hyperparathyroidism.—Garloch [31] discusses hyperparathyroidism and particularly the danger of confusing it with polyostotic fibrous dysplasia. A case illustrating this point is discussed in detail. The conclusions drawn are that a too hasty diagnosis of hyperthyroidism should not be made even when the values for calcium and phosphorus are outside normal limits and there is a negative calcium balance. If doubt exists as to the diagnosis a biopsy should be done of material from one of the cystic areas of bone. Pathologic examination will differentiate the two conditions.

<center>KNEE</center>

Cyst of the Internal Meniscus of the Knee. — Marchand and Guibert [32] state that cysts of the internal cartilage are much less frequent

30. Ducuing, J.: Presse méd. **46**:1225, 1938.

31. Garloch, J. H.: Ann. Surg. **108**: 347, 1938.

32. Marchand, L., and Guibert, H. L.: Ann. d'anat. path. **4**:389, 1938.

than cysts of the external cartilage. The internal cartilage is more firmly attached and is therefore more apt to tear from an injury, while the external cartilage, being loosely attached, is subjected to small traumas more productive of cyst formation. The pseudocystic degeneration usually involves the middle layer of the cartilage, and the inside of the cystic cavities has no endothelial lining. True cysts with endothelial lining are rare. The explanation of these cysts is uncertain. Some authors attribute them to embryonic inclusion of endothelial tissues in the cartilage during development, while others believe the cystic degeneration is due to trauma. A careful pathologic examination of a cyst of the internal cartilage is presented. There is an external layer of highly vascular connective tissue. The middle layer represents the external layers of the cartilage. The third is a fibrocartilaginous internal layer which is nothing but the less vascular middle zone and a portion of the avascular internal zone of the cartilage. These different zones present dissolutions of continuity of variable extent, which produce the pseudocystic effect. The formation of the pseudocyst is brought about by a swelling of the fibroblasts, the cytoplasm of which undergoes vacuolar degeneration. The enlarged cells then burst, and a cavity results, filled with a mucoid substance.

Demonstration of Articular Cartilage.—Nordheim[33] was able to demonstrate articular cartilage, particularly that of the knee, in roentgenograms by obtaining a partial vacuum in the joint by traction, abduction or adduction. He was able to demonstrate the medial meniscus in about 70 per cent of normal persons; the lateral meniscus could be demonstrated only rarely. If fluid was present in the knee it was impossible to show the meniscuses. A small amount of air injected into the joint aided in visualization of the cartilage.

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33. Nordheim, Y.: Fortschr. a. d. Geb. d. Röntgenstrahlen **57**:479, 1938.

(To Be Concluded)

DIAPHRAGMATIC HERNIA IN INFANTS

REPORT OF TWO CASES

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Congenital hernia of the diaphragm may be encountered at any stage of life and may attain a considerable size without becoming incompatible with fairly good health. It is seen frequently in the newborn and occasionally in the aged. Few infants, however, live long if obstructive symptoms develop, and most of them die within a few hours or at most a few days after birth. Furthermore, successful operative results in infants under 1 year of age are few, as may be seen from the report of Orr,[1] who in a careful survey of the literature up to 1936 found records of only 17 infants who had been operated on and of only 8 who had survived the surgical procedure.[2] One cannot read the details

From the Presbyterian Hospital.

1. Orr, T. G., and Neff, F. C.: Diaphragmatic Hernia in Infants Under One Year of Age Treated by Operation, J. Thoracic Surg. **5**:434, 1936.

2. McCleave, T. C.: Diaphragmatic Hernia, Am. J. Dis. Child. **13**:252 (March) 1917. DeBuys, L. R.: A Case of Anomaly of the Diaphragm, with Herniation into the Thorax of Certain Viscera Resulting in a Gastric and Intestinal Obstruction. ibid. **19**:55 (Jan.) 1920. Barnett, G. S.: Congenital Deficiency of the Diaphragm, Brit. M. J. **1**:602, 1921. Woolsey, J. H.: Diaphragmatic Hernia, J. A. M. A. **89**:2245 (Dec. 31) 1927. Olmsted, H. C.: Nontraumatic Lesions of the Diaphragm in Infancy and Childhood, Northwest Med. **27**:169, 1928. Meyer, W., in discussion on Harrington, S. W.: Diaphragmatic Hernia, Arch. Surg. **16**:386 (Jan., pt. 2) 1928. Bettman, R. B., and Hess, J. H.: Incarcerated Diaphragmatic Hernia in an Infant, with Operation and Recovery, J. A. M. A. **92**:2014 (June 15) 1929. Donovan, E. J.: Repair of Diaphragmatic Hernia in an Infant, S. Clin. North America **11**:517, 1931. Bettman, R., and Hess, J.: Diaphragmatic Hernia in an Infant, Ann. Surg. **93**:1274, 1931. Eggers, C.: Hernia or Eventration of the Diaphragm, J. Thoracic Surg. **1**:41, 1931. Robb, E. F.: Congenital Diaphragmatic Hernia: Successful Result, Journal-Lancet **51**:

of these reports without coming to the conclusion that the high mortality is due to the difficulty in making an early diagnosis, the trouble encountered in preparation of the baby for the operation and the technical difficulties incident to the operative procedure itself. In our limited personal experience two extremes have been met with: (1) a case in which the diagnosis was easy (being almost self evident on inspection), the problem of preoperative preparation comparatively simple, the surgical procedure involved in reduction of the abnormal contents of the thoracic cavity and repair of the defect in the diaphragm not difficult and the outcome successful, and (2) a case in which the diagnosis was impossible without roentgen examination, the preparation of the baby for the operation extremely difficult and the final outcome, after three major operations, fatal.

REPORT OF CASES

CASE 1.—R. M., a boy aged 3 months, was admitted to the Presbyterian Hospital on July 24, 1935, to the service of Dr. A. H. Parmelee, with the following history: Delivery (April 20) had been normal; the weight at birth was 8 pounds 10 ounces (3,705 Gm.). He had never been breast fed and had been given several formulas without much success. At 7 weeks of age he began to vomit and the stools became loose, conditions which persisted in spite of every effort to modify his food. During the past ten days sweetened condensed milk had been used, and the vomiting had been much less. On entrance to the hospital, examination revealed a thin baby weighing 10 pounds (4,535 Gm.). The skin was covered by a heat rash. The length was 25 inches (63.5 cm.). The chest seemed unusually prominent and the abdomen unusually flat. The area of cardiac dulness was well to the right of the sternum, and the tones were heard best in this area. Over the left side of the thorax a tympanitic note was elicited on percussion, breath sounds were indistinct, and some gurgling noises were heard with the stethoscope. The diagnosis of diaphragmatic hernia on the left was, of course, readily made. Under the fluoroscope, by plain roentgenograms and by oral administration of barium sulfate this impression was easily confirmed (fig. 1) by Dr. F. H. Squire, who reported: "The heart shadow is displaced to the right. The entire left lung field is crowded by rounded masses of decreased density, giving an exaggerated honeycomb appearance, which is more or less characteristic of air in the small bowel. There is good excursion of the diaphragm, the left side of which moves in the opposite direction (paradoxically). Barium readily enters and fills the stomach, which is rather large and lies in its normal position in the abdomen. One-half hour later barium is seen in the small bowel, many loops of which have passed through a lateral defect in the diaphragm and have occupied the entire left pleural cavity" (fig. 2).

In preparation of the baby for the surgical operation Dr. Parmelee encountered relatively little trouble. The infant was fed mostly by gavage because of cyanosis

517, 1931. Johnson, H., and Bower, A. G.: Strangulated Diaphragmatic Hernia in an Infant, California & West. Med. **36**:48, 1932. Unshelm, E.: Hernia hiatus aesophagie beim Kind, Monatschr. f. Kinderh. **51**:94, 1931. Barrett, N. R., and Wheaton, C. E. W.: Pathology, Diagnosis and Treatment of Congenital Diaphragmatic Hernia in Infants, Brit. J. Surg. **21**:420, 1934. Coryllos, A. N.: Two Cases of Diaphragmatic Hernia, S. Clin. North America **14**:285, 1934. Iizuka, F., and Sano, U.: Angeborene Zwerchfellhernie beim Säugling (mit Erfolg operierter Fall), Orient. J. Dis. Infants **11**:23, 1932.
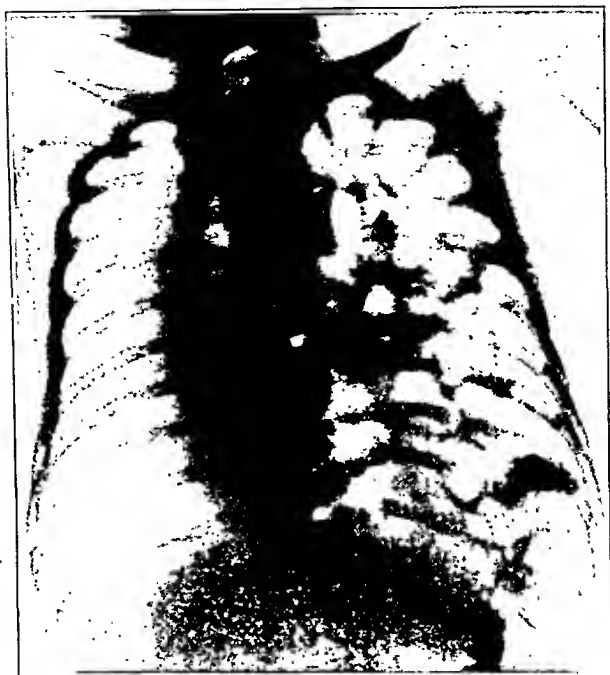
Fig. 1 (case 1).—R. M., aged 3½ months, with a diaphragmatic hernia on the left. The roentgenogram shows the appearance of the left side of the chest before the introduction of barium sulfate by mouth.

Fig. 2 (case 1).—A, portion of the defect in the diaphragm, close to the chest wall. The stomach occupies a normal position. B, barium-filled loops of bowel occupying the left pleural cavity.

and choking when the dropper was used. Progress was satisfactory, and by August 1 (eight days after admission) he had gained 3½ ounces (99 Gm.). The next day, however, he showed a drop in weight, and it was decided that further delay in operating was unwise. The blood count showed: hemoglobin, 80 per cent; red cells, 4,850,000; white cells, 9,500. On August 2, therefore, after a blood transfusion of 90 cc. had been given intravenously by scalp vein, operation was performed (by Dr. Miller). In view of the experience of other surgeons with similar problems, the combined thoracic and abdominal approach seemed logical. With the child under ether anesthesia the abdomen was opened through an oblique incision parallel to the costal border on the left. The left side of
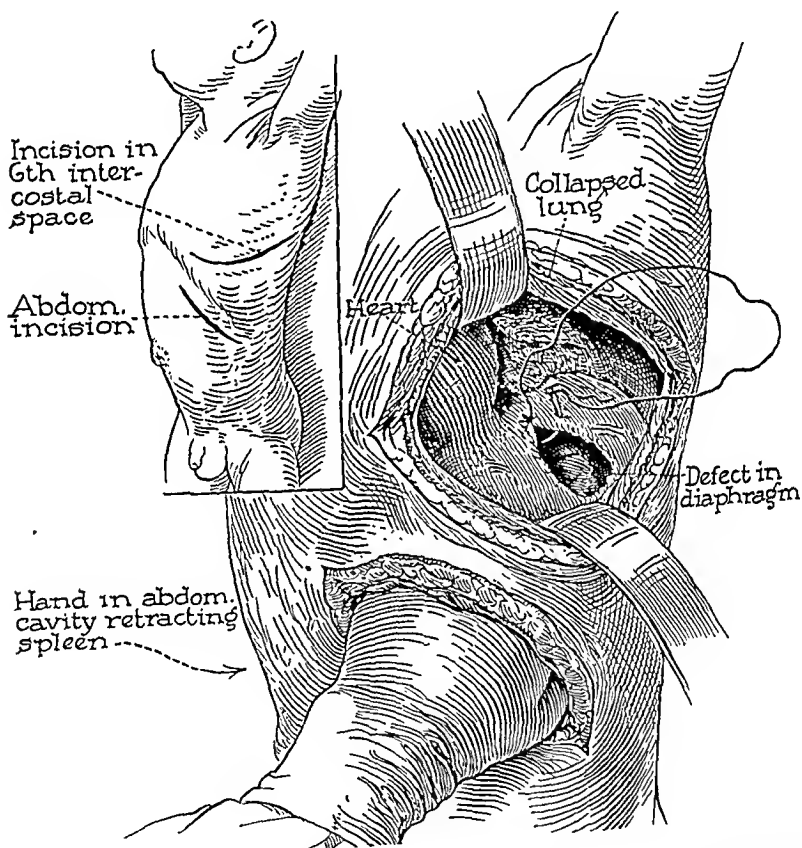
Fig. 3 (case 1).—Method of closure of the defect in the left side of the diaphragm after reduction of the small bowel and the colon into the abdomen.

the chest was then opened by a long incision through the sixth interspace, and the margins were widely retracted. There was, of course, no need for positive pressure anesthesia, because the lung on this side had long since been collapsed. The left side of the chest was completely filled with loops of small bowel; most of the colon was also present. The cecum and appendix lay near the apex of the cavity. The heart was pushed markedly to the right, and beyond it, through the mediastinal pleura, could be seen the pink, aerated right lung, working easily. The collapsed left lung could be recognized as a small purple mass at the hilus. In order to reduce the displaced loops of bowel through the defect in the diaphragm, it was necessary for the surgeon to introduce his left hand into the abdomen and spread the opening with two fingers while with the right hand he gently pushed first the colon and then the loops of small bowel through the
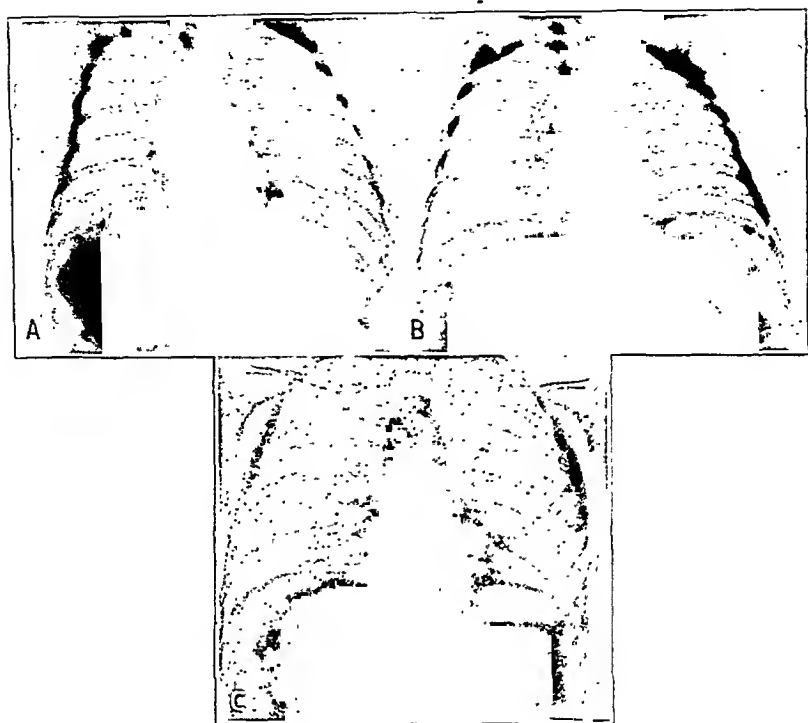
Fig. 4 (case 1).—*A*, roentgen appearance of the chest one day after the operation. Note the air partly filling the left pleural cavity. *B*, appearance of the chest three weeks after the operation. Note the complete expansion of the left lung and the normal curve of the diaphragm. *C*, roentgenogram taken two years and eight months after the operation.

Fig. 5 (case 1).—Photograph of R. M., taken two years and eight months after the operation.

opening. The spleen was the organ which interfered most with this maneuver, as it lay snugly in the defect. The defect was trianglar, its base being against the lateral wall of the chest and each side being about 2½ inches (6.2 cm.) long. Repair was easily made from the thoracic side (fig. 3); a running catgut suture was used, which effectively brought the sides of the defect together without tension. The long opening in the wall of the chest was then quickly closed after interrupted catgut sutures had been placed around the adjacent ribs and fine catgut in the margins of the intercostal muscles. The several loops of intestine, which during this closure had been kept warm with pads, were gently reduced within the abdomen, and the incision was brought together in the usual way.

The postoperative course was remarkably uneventful. Small feedings of breast milk were quickly resumed by gavage and were well taken. Breathing became easier and more regular. Roentgenograms of the chest, taken on the following day (fig. 4 *A*), showed a more nearly normal position of the heart and expansion of the upper half of the left lung. By the third day the lung markings in the lower half were visible, and at the end of three weeks (fig. 4 *B*) the chest appeared normal. On the fifth day the baby showed a red throat and high fever, which gradually subsided, and at the end of two weeks he began to gain in weight. Both incisions healed without infection, and the child was discharged from the hospital, looking well and happy, exactly one month after admission. His weight was 11 pounds 2½ ounces (5,060 Gm.). Since that time almost three years has elapsed, and he has grown to be a strong, healthy lad (fig. 5), with no abnormality shown by either direct or roentgen examination.

In contradistinction to this experience we present our second case, representing the opposite extreme: difficulty in diagnosis, difficulty in preoperative preparation, great difficulty in the operative procedures and finally, fifteen months after the first of seven admissions to the hospital, death from bronchopneumonia.

CASE 2.—J. B., a girl aged 19 days, was admitted to the Presbyterian Hospital, to the service of Dr. H. N. Sanford, on Feb. 29, 1936. She was born at home, the weight at birth being 7½ pounds (3,401 Gm.). The mother stated that two days after birth she had a violent choking attack and became cyanotic. Complementary feedings had been used. She had vomited frequently and had become cyanotic after each feeding. Examination on admission revealed an emaciated infant weighing 6 pounds 5 ounces (2,862 Gm.). She was slightly cyanotic. The blood count showed: hemoglobin, 80 per cent; red cells, 4,000,000; and white cells, 27,000, per cubic millimeter. No gross abnormalities could be made out, and the thoracic findings gave no clue to the presence of a diaphragmatic hernia. A flat roentgenogram of the chest, however, revealed a rounded air-containing pocket immediately behind the heart (fig. 6 *A*). When barium was given by mouth (March 5) it passed through a tortuous, dilated esophagus into a totally intrathoracic stomach, which when filled occupied the area just behind the heart and over the right dome of the diaphragm (fig. 6 *B*). The infant was given breast milk by gavage for a few days and then evaporated milk, water and sugar (eight feedings by bottle in twenty-four hours, with cod liver oil and orange juice). On March 21, when she left the hospital, she had gained, weighing 7 pounds 13 ounces (3,543 Gm.).

She was returned to the hospital about three weeks later (April 15), weighing 8 pounds 13 ounces (3,997 Gm.). She had done fairly well at home. There had been one attack of vomiting of coffee-like material and slight regurgitation after each feeding. The formula was changed to full strength lactic acid milk every

four hours, and she was discharged on April 21, weighing the same as on admission. On May 5 (about two weeks later) she was brought to the hospital for the third time. She had not done well at home; she vomited after almost every feeding and had lost 5 ounces (141.5 Gm.) in weight. Every effort was exerted during the next seven weeks to prepare her properly for operation, but great difficulties were encountered. However, by June 25 a gain of 1 pound 7 ounces (651 Gm.) had been accomplished; the blood count showed a hemoglobin content of 75 per cent; there were 4,900,000 red cells and 13,200 white cells per cubic millimeter, and after a small transfusion of blood from the father it was decided to proceed with the operation.

Operation was performed by Dr. Miller on June 25. The surgical approach in this case, of course, was different from that in the preceding case. Instead of an open defect in the diaphragm without any sac between the left upper quadrant of the abdomen and the left side of the chest, we were dealing with a paraesophageal hernia with a large sac occupying the mediastinum and a narrow neck near the midline. With the baby under ether anesthesia a left rectus incision
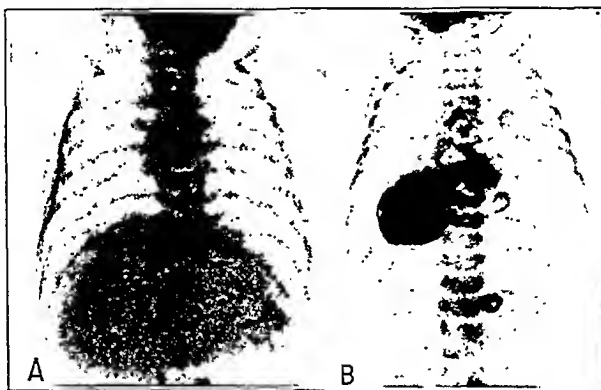
Fig. 6 (case 2).—*A*, roentgenogram of J. B., aged 19 days, with a paraesophageal hernia of the diaphragm. Note the round air-containing pocket immediately behind the heart. *B*, roentgenogram taken when the baby was 3 weeks old, showing the position of the stomach after the introduction of barium sulfate.

was made. The right lobe of the liver was retracted to the right of the aorta. In this opening lay the duodenum, and traction on it brought into view the greater curvature of the stomach. It was grasped with a Babcock forceps, and the entire stomach was gently and easily reduced to its normal position in the abdomen. The condition of the baby suddenly became very poor, and it was necessary rapidly to insert a running catgut suture to approximate the edges of the ring and effectively close the neck of the hernial sac. The postoperative progress was fair for several days, and the temperature ranged between 101 and 102 F. The child took small feedings by dropper fairly well, but at the end of a week the temperature was 104 F. and vomiting recurred. Fluoroscopic examination showed clouding of the lower half of the right lung field. On July 4, nine days after the operation, the condition was critical, and it was apparent from the rapid loss of weight, the obstructive symptoms and the vomiting of brown material that a recurrence of the herniation had occurred and that nothing short of an emergency operation could forestall a fatal result. Consequently, after this

diagnosis had been confirmed by introduction of a little barium sulfate through a tube, the baby was taken to the operating room, and under local anesthesia the abdomen was reopened, just to the right of the midline. The child's condition was very poor, and it was not easy to drag the swollen stomach down a second time through the neck of the sac, the margins of which were very edematous. During this maneuver several ounces of brown fluid escaped from the nose and mouth, and it was thought that the baby would die on the table. Very hurriedly a few interrupted stitches were inserted to narrow the neck of the sac, the liver was placed against this area and the stomach was anchored in position (fig. 7). The abdomen was quickly closed. The postoperative course was exceedingly stormy, and nothing but extreme effort on the part of the special nurses and the resident physicians of the pediatric and the surgical staff prevented death during
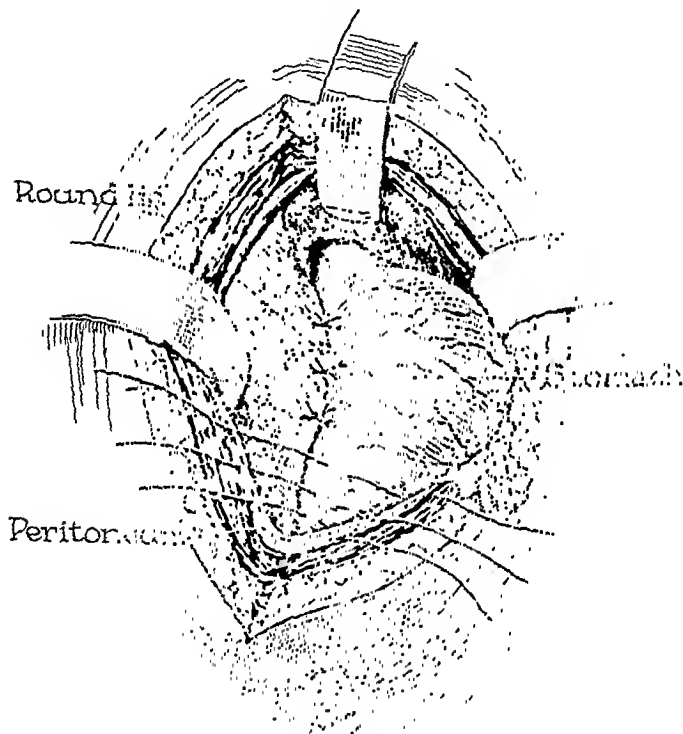
Fig. 7 (case 2).—Method of anchoring the stomach within the abdomen. Interrupted sutures of catgut were placed between the anterior wall of the stomach and the round ligament of the liver and also to the anterior parietal peritoneum.

the next few days. A Levine tube was constantly in place; the upright (almost sitting) position was maintained, and nourishment was introduced solely by vein and under the skin until a turn for the better was seen. When improvement had begun, small feedings of breast milk were given every two hours and 90 cc. of blood was given daily. The temperature remained constantly in the neighborhood of 105. The condition gradually improved for about a week, after which there was evidence of an infection of the upper part of the respiratory tract, succeeded by bronchopneumonia. For days the baby lay constantly under a steam tent; the signs of pneumonia gradually disappeared, and the temperature returned to normal. It goes without saying that we were all concerned over the question of the position of the stomach during this critical period. As soon, therefore, as the baby started to gain weight a small amount of barium sulfate was introduced and the position of the stomach within the abdomen verified (fig. 8). On September 25, eleven

weeks after the second operation, the child weighed 11 pounds 9 ounces (5,243 Gm.) and was discharged from the hospital.

Not long after this we began to consider reporting this case as one in which the operation was successful, but decided to wait until the baby had become entirely well and roentgen studies could be made to establish evidence of our success. This decision proved to make the difference between the report of a success and the report of a failure.
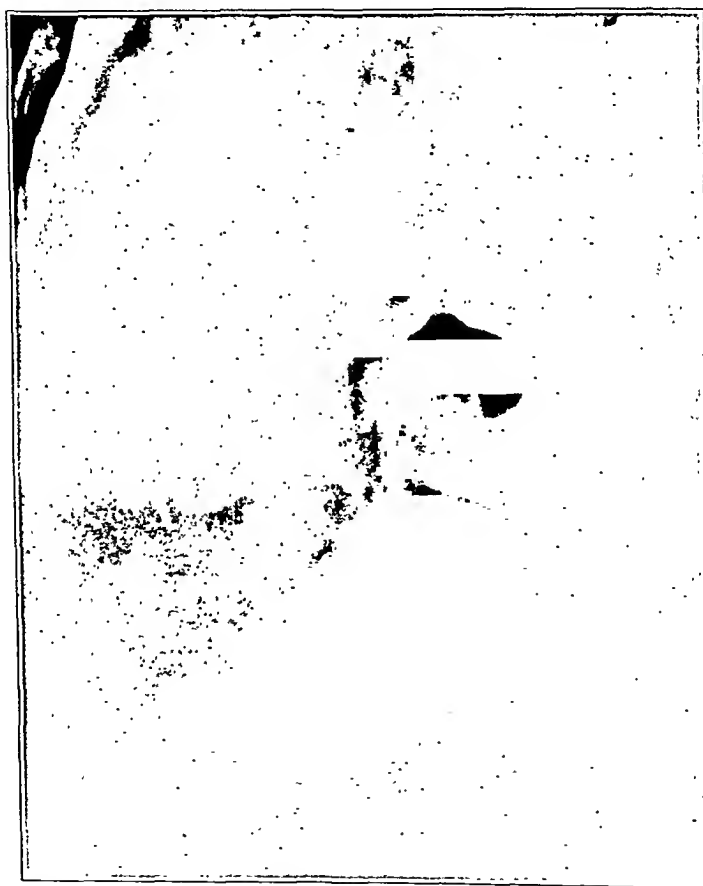
Fig. 8 (case 2).—Roentgenogram taken two and one-half months after the second operation. Note the dilated esophagus, the intra-abdominal position of the stomach and the air-containing loops of bowel occupying the hernial sac.

On November 16 the baby, now 9 months old and weighing 14 pounds 11 ounces (6,660 Gm.) was returned to the hospital for observation. She had done well at home until the last few days, when she had become feverish and had vomited a little. She was able to sit up alone, and she had two teeth. Her food was evaporated milk, water and sugar, two cereals, vegetables and one egg. The hemoglobin content of the blood was 80 per cent; the red cell count was 3,900,000 and the white cell count 7,000 per cubic millimeter. Severe bronchitis was present,

which accounted for the fever; this cleared up in a week, and she was discharged from the hospital on November 2, weighing 14 pounds 2 ounces (6,406 Gm.).

About five weeks later (December 30) she was again brought to the hospital (fifth admission) because during the past week she had vomited more or less after each feeding, her appetite was poor, there was a slight cough and she had lost 1 pound (453 Gm.) in weight. This time she remained in the hospital thirteen days, during which period the temperature returned to normal and the weight to 14 pounds 12 ounces (6,689 Gm.).

Three months later (April 5, 1937) she was again brought to the hospital, this time because of painful bowel movements and black stools. She was 14 months old and weighed 16 pounds 5 ounces (7,398 Gm.). After observation for twelve days she was discharged in fair condition, with only occasional vomiting and a

Fig. 9 (case 2).—Roentgenogram showing the faint outline of the hernial sac above the right side of the diaphragm.

constant weight. On May 22 she entered the hospital for the seventh and last time. Her age was 15 months and 12 days, and she weighed 17 pounds 6 ounces (7,881 Gm.) but she had not been doing well, in spite of the fact that her condition was fair. Her appetite had been fairly good and she ate regularly, but she had great difficulty with her bowels and great pain on passage of the stools, Roentgen examination (May 24) showed the heart deviated to the left; the lower half of the right lung field showed clearly the curved margin of the hernial sac (fig. 9) and within it several loops of bowel. Consultations resulted in a decision to operate again, with the object of reducing the contents of hernia, and, if possible, of closing the neck of the sac. On May 25 the abdomen was reopened through the old left rectus incision. The stomach was found to be in its normal position, entirely within the abdomen. It was lifted upward and retracted toward the right; this exposed the neck of the hernial sac, into which and from which led the trans-

verse colon (fig. 10). It had become so tightly wedged into the opening that it was reduced with considerable difficulty. It measured in length approximately 12 inches (33 cm.). The walls were edematous, and within the lumen could be felt some firm inspissated material. Closure of the neck of the sac was accurately made with a running suture of silk. Death occurred on the following day.

Autopsy.—There was paraesophageal hernia on the right, with an empty sac about the size of a large orange occupying the mediastinal space immediately behind and to the right of the heart. The stomach occupied a normal position; it was adherent anteriorly to the parietal peritoneum. There was no peritonitis. The neck of the hernial sac was completely closed except for an opening close
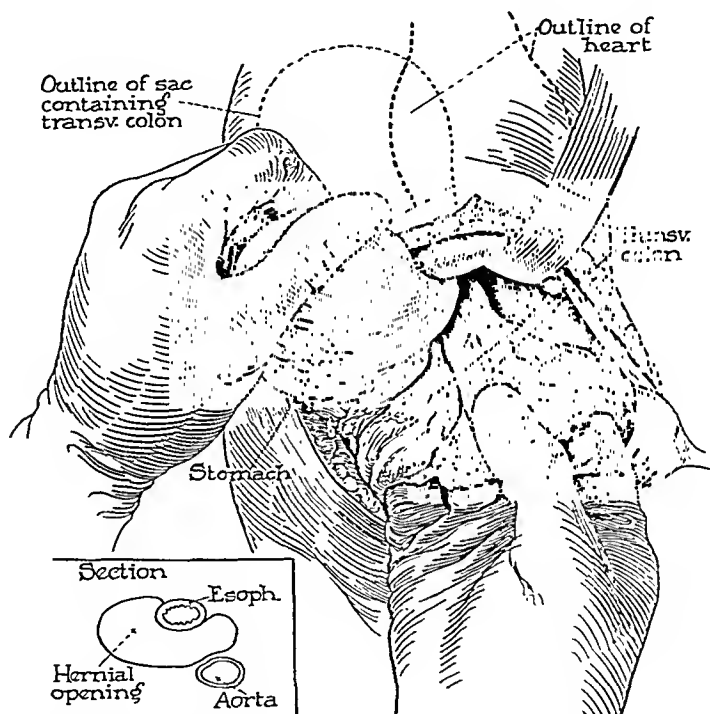
Fig. 10 (case 2).—Segment of the transverse colon in the hernial sac formerly occupied by the stomach.

to the spine, which admitted the tip of the finger. There was extensive broncho-pneumonia of the left lung.

COMMENT

This second case illustrates the importance of making a snug closure of the neck of the hernial sac with nonabsorbable suture material; our failure to accomplish this at the first operation was responsible, we believe, for the trouble which followed later. It illustrates, also, the effectiveness of a method of anchoring the stomach in its normal position. If this also had been done at the first operation, the result might have been a success.

LESIONS OF THE SUPRASPINATUS TENDON AND ASSOCIATED STRUCTURES

INVESTIGATION OF COMPARABLE LESIONS IN THE HIP JOINT

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During a study of lesions in 150 shoulder joints, observations were made with regard to the abduction phase of shoulder motion which serve to corroborate the teachings of a small group of contemporary anatomists.

1. Abduction of the arm is a complex mechanism, involving the scapulohumeral, the acromioclavicular and the sternoclavicular joint, whereby the scapula moves along the chest wall, the humeral head glides within the glenoid cavity and the clavicle rotates as its lateral end moves dorsalward, the glenoid moving forward and upward. Toward the completion of abduction there is ipsilateral curvature of the dorsolumbar portion of the spine. In the bared specimen these joints demonstrate a range of motion far in excess of that normally required to elevate the arm.

2. Complete abduction can be obtained in the coronal plane only by external rotation of the humerus (Martin [1]) and in the sagittal plane by internal rotation of the humerus (Codman; [2] McGregor [3]). As the bared upper extremity of a human cadaver is elevated, one notes that the greater tuberosity glides posteriorly beneath the coracoacromial ligament and the acromion process where the interval between these structures and the humeral head is increased, carrying the humerus into external rotation; and as the arm is elevated in the sagittal plane, one observes that the lesser tuberosity abuts against the anterior part of the coracoacromial arch and glides internally, carrying the humerus into internal rotation. These movements are assisted by the gliding mechanism of the interposed bursae.

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1. Martin, C. P.: A Note on the Movements of the Shoulder-Joint, Brit. J. Surg. 20:61, 1932.

2. Codman, E. A.: The Shoulder: Rupture of the Supraspinatus Tendon and Other Lesions In or About the Subacromial Bursa, Boston, The Author, 1934.

3. McGregor, L.: Rotation at the Shoulder: A Critical Inquiry, Brit. J. Surg. 24:425, 1937.

3. By roentgenographic and fluoroscopic studies of the shoulder girdle in varying stages of abduction (fig. 1) it is observed that the scapula begins to move at the very onset of elevation of the arm from the side and that motion occurs in the scapulohumeral joint above the
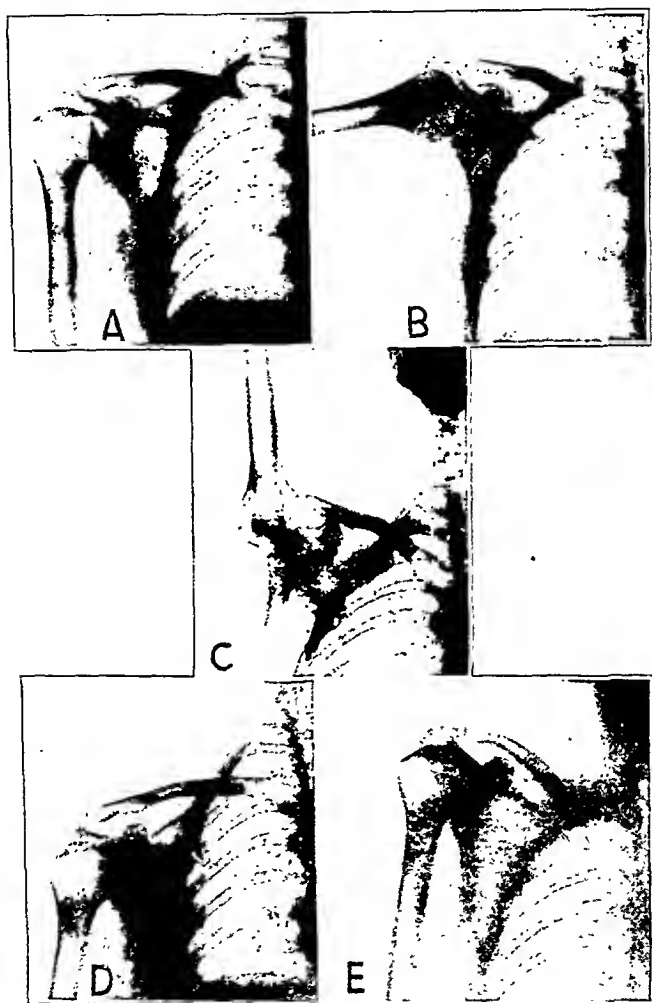
Fig. 1.—Normal shoulder girdle of a man aged 30. At *A* is shown the arm at rest at the side; at *B*, abduction to the horizontal plane; at *C*, complete abduction (pivotal position). Comparison of the position of the spine or vertebral border of the scapula in *A* and *B* indicates that the scapula rotates below the horizontal plane, while comparison of the amount of articular surface of the humerus that has left the glenoid cavity in *B* and *C* indicates motion of the scapulohumeral joint above this plane. (After Lockhart.)

At *D* is shown the maximum depression and at *E* the maximum elevation of the shoulder girdle without scapulohumeral motion, indicating the reserve range of motion possible in the sternoclavicular and acromioclavicular joints, which exceeds that required in complete abduction normally (*A* to *C*).

horizontal plane. This confirms the observations of Cathcart[4] and Lockhart.[5]

4. To analyze the function of the individual muscular components involved in abduction, cases of isolated paralysis of the deltoid, the trapezius, the serratus anterior and the supraspinatus muscle and recent tears of the last-named muscle were analyzed from the literature and from my own clinical material.

The importance of the action of the supraspinatus muscle in furnishing a fulcrum for the humeral head in the glenoid cavity for the action of the deltoid muscle has been stressed by Stevens[6] and by Codman. Early, in its absence, abduction cannot be initiated. The fact that abduction is restored in cases of long-standing involvement despite the persistence of demonstrable tears of the supraspinatus muscle (Codman) indicates that one or more of the other short rotators may effectively assume the function of the supraspinatus muscle.

In the presence of localized paralysis of the deltoid muscle due to injury of the circumflex nerve (Smith and Christensen[7]) the arm cannot be abducted at the shoulder joint even with the supraspinatus muscle intact. In cases of involvement of long duration this deficiency is partially overcome by substitutionary action, especially of the long heads of the biceps and the triceps muscle. Abduction by action of the supraspinatus muscle alone, as reported by Duchenne[8] and Codman, is unusual.

The trapezius and the serratus anterior muscle become active immediately as the arm leaves the side. In the presence of isolated paralysis of the former muscle (Lockhart,[5] Beevor[9]) there are slight "winging" and weakness in the early stage of abduction, which disappear as the mechanical efficiency of the serratus anterior muscle increases. In the presence of isolated paralysis of the serratus anterior muscle, "winging" is marked, and abduction is limited below the horizontal plane. The

4. Cathcart, C. W.: Movements of the Shoulder Girdle Involved in Those of the Arm on the Trunk, J. Anat. & Physiol. 18:211, 1884.

5. Lockhart, R. D.: Movements of the Normal Shoulder Joint and of a Case with Trapezius Paralysis Studied by Radiogram and Experiment in the Living, J. Anat. 64:288, 1930.

6. Stevens, J. H.: The Action of the Short Rotators on the Normal Abduction of the Arm with a Consideration of Their Action in Some Cases of Subacromial Bursitis and Allied Conditions, Am. J. M. Sc. 138:870, 1909.

7. Smith, J. F., and Christensen, H. H.: Deltoid Paralysis Following Shoulder Injuries, Surg., Gynec. & Obst. 41:451, 1925.

8. Duchenne, G. B.: Physiologie des mouvements, Paris, J. B. Baillière et fils, 1867.

9. Beevor, C. E.: The Croonian Lectures on the Central Nervous System, Brit. M. J. 1:1357, 1903.

protagonistic action of the long head of the triceps muscle to abduction has been stressed elsewhere (Horwitz and Tocantins[10]).

5. The "neutral position" is necessary in the treatment of injuries to the shoulder to place the shoulder muscles at rest, to prevent contractures and to place the arm in a functional position if it stiffens. This requires that the arm be (1) in the horizontal plane, (2) in the plane of the scapula, i. e., 30 degrees anterior to the coronal plane of the body, to avoid torsion of the inferior capsule (Johnston[11]) and tension of the pectoralis major muscle (Böhler[12]), and (3) rotated to a position 45 degrees less than that of complete external rotation, since the arc of rotation of the arm in the horizontal plane is 90 degrees (Codman). Since abduction has been shown to continue in the scapulohumeral joint from 20 to 30 degrees above the horizontal plane, it is logical to recommend this extent of abduction (120 degrees), suggested by Mayer[13] after surgical correction of rupture of the supraspinatus tendon, to insure approximation of the tendinous ends.

PATHOLOGIC FINDINGS

As acknowledged by Codman,[14] Smith[15] in 1834 reported 7 instances of destruction of the upper part of the shoulder capsule in 40 anatomic dissections, 5 of these involving the musculotendinous cuff. Akerson, cited by Codman,[2] found 64 tears of the supraspinatus tendon in 200 shoulder joints (32 per cent) and associated tears in other portions of the musculotendinous cuff in 30 instances. The injury was most frequent in males (2:1) and was bilateral in 14 of the first 100 specimens. Keyes[16] noted 24 tears of the supraspinatus tendon in 192 shoulder joints (17 per cent). The patients were equally divided as to sex; the youngest was 45 years old and the average age was 53. Skinner[17]

10. Horwitz, M. T., and Tocantins, L. M.: Isolated Paralysis of the Serratus Anterior (Magnus) Muscle, J. Bone & Joint Surg. **20**:720, 1938.

11. Johnston, T. B.: The Movements of the Shoulder Joint: A Plea for the Use of the "Plane of the Scapula" as the Plane of Reference for Movements Occurring at the Humeroscapular Joint, Brit. J. Surg. **25**:252, 1937.

12. Böhler, L.: The Treatment of Fractures, ed. 4, translated by E. W. H. Groves, Baltimore, William Wood & Company, 1935.

13. Mayer, L.: Rupture of the Supraspinatus Tendon, J. Bone & Joint Surg. **19**:640, 1937.

14. Codman, E. A.: Rupture of the Supraspinatus—1834 to 1934, J. Bone & Joint Surg. **19**:643, 1937.

15. Smith, J. S.: Pathological Appearance of Seven Cases of Injury of the Shoulder Joint, with Remarks, Am. J. M. Sc. **16**:210, 1835; London M. Gaz. **14**:280, 1834.

16. Keyes, E. L.: Anatomical Observations on Senile Changes in the Shoulder, J. Bone & Joint Surg. **17**:953, 1935.

17. Skinner, H. A.: Anatomical Considerations Relative to Rupture of the Supraspinatus Tendon, J. Bone & Joint Surg. **19**:137, 1937.

observed 6 such tears in 100 shoulder joints, and Fowler [18] in a series of 340 specimens noted 1 complete tear of the supraspinatus tendon in every 28 and 1 incomplete tear in every 6 shoulder joints.

While the clinical features of tear of the supraspinatus tendon have been stressed by Codman, this careful observer up to 1934 had never observed a tear less than three weeks after injury and admitted that, although this clinical diagnosis had been corroborated at the operating table in 29 cases, in 16 others no such lesion could be demonstrated.[18a] Wilson [19] in 1931 reported the demonstration of tears of the supraspinatus tendon at the operating table in 10 instances. These defects, varying in size from 1 to 2½ inches (2.5 to 6.3 cm.) in diameter, occurred in patients in the fourth decade of life, except in 1 case, in which the patient was 35. Recent tears have been demonstrated by Ferguson [20] four days after injury, by Mayer [13] forty-eight hours after injury and by Davis and Sullivan [21] in 5 cases within seventeen days after the initial trauma. In 12 cases, reported by Outland and Shepherd,[22] 1 lesion in a patient aged 32 and 2 in patients aged 42 followed dislocation of the shoulder The ages of the remaining patients ranged above 50.

PERIARTICULAR AND ARTICULAR CHANGES IN THE SHOULDER JOINT

Of the 75 cadavers (150 shoulder joints) utilized in this study, 71 were male and 4 female. The average age at death was 55, the ages varying from 35 to 82.

1. *Changes in Bursae (Subacromial; Subdeltoid; Subcoracoid).*— In 30 specimens variable changes were noted, with thickening of the walls, villous formation and partial or complete obliteration of the bursal cavity. In 10 specimens the cavity of the bursa communicated with the shoulder joint owing to a complete defect in the bursal floor, i. e., tear of the supraspinatus tendon. In 3 specimens, in each of which

18. Fowler, E. B.:   Stiff, Painful Shoulders, Exclusive of Tuberculosis and Other Infections, J. A. M. A. **101**:2106 (Dec. 30) 1933.

18a. In a recent contribution, Codman reported a fresh rupture of the supraspinatus tendon, diagnosed forty-eight hours after, and visualized seven days after, injury (Codman, E. A.:   Rupture of the Supraspinatus, Am. J. Surg. **42**:603 [Dec.] 1938).

19. Wilson, P. D.:   Complete Rupture of the Supraspinatus Tendon, J. A. M. A. **96**:433 (Feb. 7) 1931.

20. Ferguson, L. K.:   Suture of Ruptured Supraspinatus Tendon Four Days After Injury, Am. J. Surg. **29**:294, 1935.

21. Davis, J. W., and Sullivan, J. E.:   Rupture of· the Supraspinatus Tendon, Ann. Surg. **106**:1059, 1937.

22. Outland, T. A., and Shepherd, W. F.:   Tears of the Supraspinatus Tendon, Ann. Surg. **107**:116, 1938.

the subcoracoid bursa was separated from the main subacromial (sub-deltoid) bursa by a complete partition, the former showed degenerative changes, a large calculus filling it in 1 instance, while the subacromial bursa appeared normal. In no other instance were calcium deposits found within or about the bursae.

2. *Changes in the Musculotendinous Cuff (Supraspinatus, Infraspinatus, Teres Minor, and Subscapularis Tendons).*—There were 10 complete tears of the supraspinatus tendon (6.67 per cent), the cavity of the subacromial bursa communicating directly with the shoulder joint. From the standpoint of statistical evaluation it is noteworthy that only
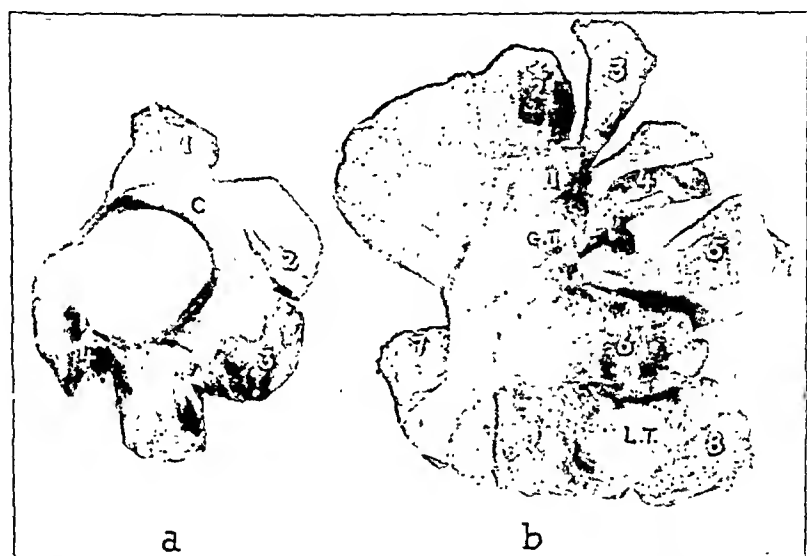
Fig. 2.—At *a* is shown the musculotendinous cuff merging intimately with the joint capsule (*C*) about the anatomic neck of the right humerus, as viewed from the articular side (*1*, supraspinatus muscle; *2*, infraspinatus muscle; *3*, teres minor muscle; *4*, subscapularis muscle). At *b* is shown the musculotendinous cuff (*2* to *6* inclusive) encircling the neck of the left femur, as viewed posteriorly. Bursae cover the great trochanter (*G.T.*) and the lesser trochanter (*L.T.*). Point *1* indicates the gluteus medius muscle; point *2*, the gluteus minimus muscle; point *3*, the piriformis muscle; point *4*, the superior gemellus, the obturator internus and the inferior gemellus muscle; point *5*, obturator externus muscle; point *6*, the quadratus femoris muscle; point *7*, the vastus lateralis muscle; and point *8*, the psoas major muscle.

1 such tear was observed in the first 100 shoulder joints studied, the other 9 being uncovered in the next 50 specimens. These tears were bilateral in 3 and unilateral in 4 cadavers. Six involved the right side

and 4 the left. All occurred in males, the youngest of whom was 50.[22a] The average age for the series of 10 (figs. 3 and 4) was 58.

In no instance was there gross evidence of calcific deposits in or about the supraspinatus tendon, although roentgenographic and microscopic studies might have revealed small deposits (Keyes[16]). In 49 specimens the upper (cephalic) portion of the musculotendinous cuff showed variable amounts of thinning, measuring in some instances only 1 to 2 mm. In 30 cases the superficial surface of the supraspinatus ten-

Tears of the Supraspinatus Tendon

	Extent of Lesion	Shape	Changes in Other Portions of Musculo-tendinous Cuff	Changes in Bicipital Tendon	Changes in Bone
1	Complete in thickness and entire width of tendon	Circular	Fibrillation and fraying of subscapularis and infraspinatus muscle	Flattening and fraying	Hypertrophic marginal articular changes; recession of great tubercle
2	Complete in thickness and entire width of tendon	Oval, in long axis of tendon	Tear of subscapularis and thinning of infraspinatus muscle	Complete tear; proximal portion absent and distal portion attached to lesser tubercle	Hypertrophic changes about tubercles and margins of bicipital groove
3	Complete in thickness but involving only partial width of tendon	Oval	Fraying and incomplete tears ("rim rents") of deep surface of subscapularis muscle	Proximal portion attached to articular surface; distal portion attached to lesser tubercle	Hypertrophic changes about tubercles and margins of bicipital groove
4, 5, 6, 7 and 8	Complete in thickness but involving width only partially	Oval	Fraying and incomplete tears of deep surface of subscapularis muscle	Flattening, fraying and thinning	Proliferative changes less marked
9	Complete in thickness; 6.5 mm. wide	Triangular	Slight fraying of subscapularis tendon	Slight fraying	Slight
10	Complete in thickness; 5 mm. wide	Semi-circular	Large gap between supraspinatus tendon and subscapularis tendon, which were frayed and thinned	Flattening and fraying	Moderate proliferative and recessive changes

don was frayed and fibrillated, with separation of the tendon fibers to form bands or "straps" (Codman). In many of these cases fissures ("rim rents") of the deep, or articular, surface of the tendon were noted. In these cases involvement of the subscapularis tendon was almost as advanced, while changes in the infraspinatus tendon were less marked, and in the teres minor tendon they were usually absent (figs. 3 and 4).

22a. In a study of 100 additional human shoulder joints, 7 complete defects of the supraspinatus tendon were disclosed, all in males, occurring bilaterally in 2 cadavers and unilaterally (right) in 3. The total incidence of tears of the supraspinatus tendon is 17 instances in 250 shoulder joints, or 6.8 per cent.

3. *Changes in the Biceps Tendon and Bicipital Groove.*—In 75 specimens the portion of the long bicipital tendon within the groove was constricted, although it was otherwise normal. In 30 instances varying stages of flattening. thinning, fraying, fibrillation and tearing were evident, such changes being usually associated with bony changes about the tubercles and the bicipital groove (fig. 5). There were 4 complete tears, and in each the proximal end of the distal portion had become
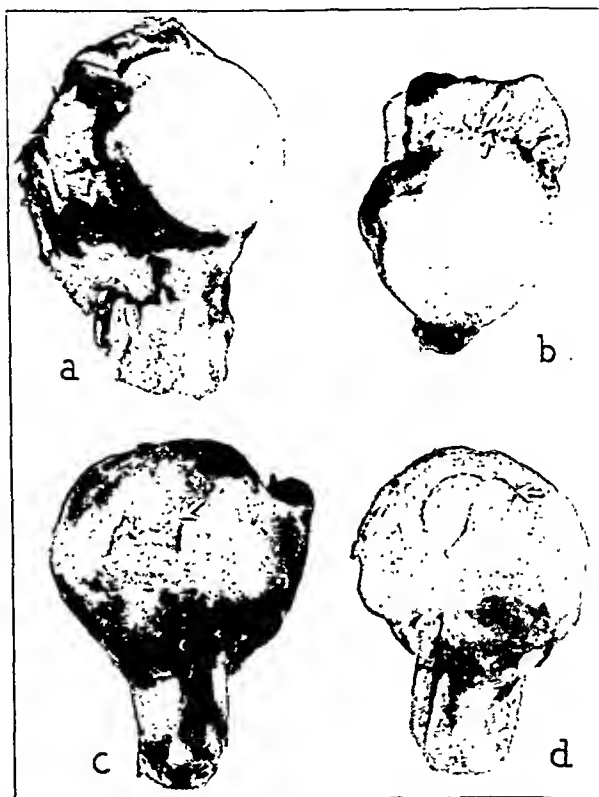
Fig. 3.—At *a* is shown fraying, fibrillation and thinning of the deep surface of the tendons of the supraspinatus, infraspinatus and subscapularis muscles; at *b*, longitudinal fissures ("rim rents") of the deep surface of the reflected supraspinatus tendon; at *c*, a triangular defect ¼ inch (6.5 mm.) wide, near the insertion of the supraspinatus tendon, the greater tubercle being exposed and showing early recessive changes; at *d*. a complete defect in the supraspinatus tendon, ½ by 1 inch (25 by 12.5 mm.) with the exposed biceps tendon flattened and frayed. The adjacent portion of the cuff is thinned and its deep surface frayed and fibrillated.

dislocated medially out of the groove and attached to the region of the lesser tubercle. In 1 of these specimens the proximal portion had completely disappeared; in 2 a small stub remained attached to the supra-

glenoid tubercle, while in the fourth the proximal portion had become attached to the articular surface of the humerus like a ligamentum teres (fig. 5). In one instance the tendon was firmly bound down within its groove by adhesions.

4. *Bony Changes.*—These seemed proportional to the amount of alteration in the soft tissues. Proliferative changes (fig. 6) involved especially the greater and lesser tubercles and the margins of the bicipi-
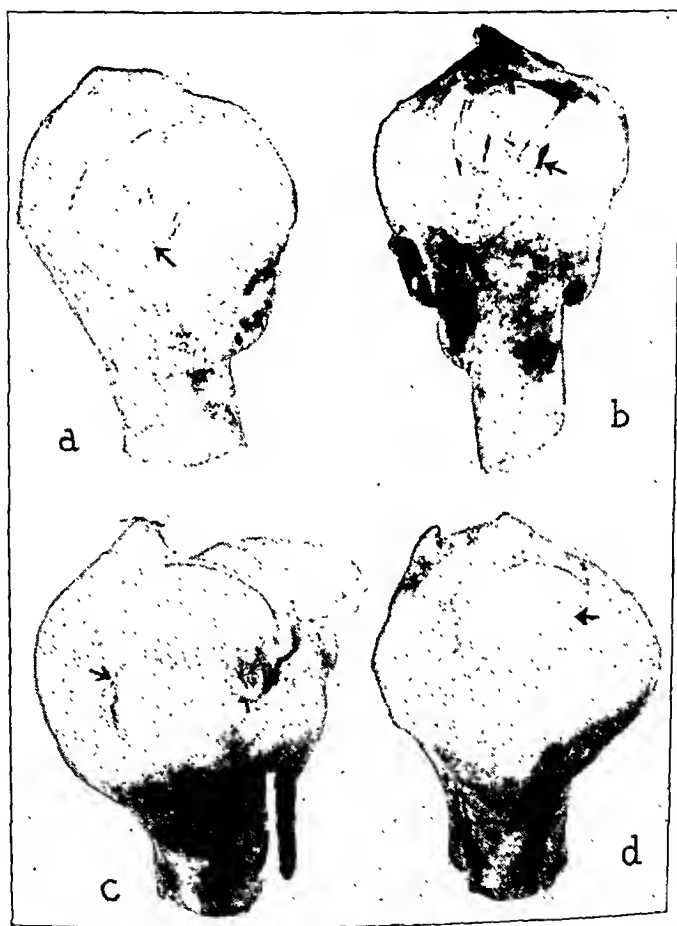
Fig. 4.—At *a* is shown complete defect in the supraspinatus tendon, 1 inch (25 mm.) in its widest diameter, with fraying and the formation of bands or "straps." The greater tubercle is exposed, with hypertrophic and recessive changes. At *b* is shown a complete defect measuring 1 by ¼ inch (25 by 6.5 mm.), with formation of "straps." The adjacent cuff is thinned and frayed on its deep surface. Note the recessive changes in the exposed greater tubercle. At *c* is shown a large gap existing between the remains of the supraspinatus tendon and the subscapularis tendon. A semicircular, complete defect is present in the supraspinatus tendon close to its insertion. At *d* is shown the largest defect uncovered in the supraspinatus tendon. The defect was circular and measured 1 and ¼ inches (31 mm.) in diameter. The remainder of the cuff was thinned and fibrillated. The biceps tendon was flattened and frayed.

tal groove, occasionally encasing the long biceps tendon. When the latter tendon had been dislocated or torn the bicipital groove had become shallow or obliterated. In instances in which, owing to a large defect in the cephalic portion of the musculotendinous cuff, the greater tubercle was exposed there was evidence of bony recession and atrophy. Similar changes on the under surface of the acromion process evidenced the effects of long-continued friction between these bony surfaces. In many of the same cases the articular cartilage showed degenerative changes, with marginal lipping most marked at the superior and anterior borders. Occasionally the cartilage was denuded in areas, with
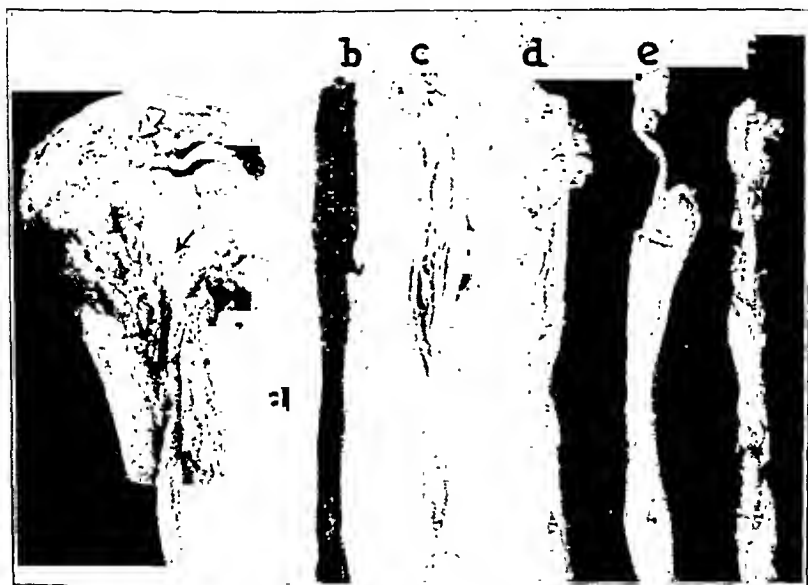
Fig. 5.—At *a* is shown the long bicipital tendon completely severed, the proximal segment having reattached itself to the articular surface and the distal segment to the lesser tubercle. Note the recession of the greater tubercle, marginal proliferation and obliteration of the bicipital groove. The tendons lettered from *b* to *f* are long bicipital tendons showing varying stages of flattening, fibrillation, fraying and tearing.

exposure of the underlying bone, which was often eburnated and glistening owing to constant friction.

PERIARTICULAR AND ARTICULAR CHANGES IN THE HIP JOINT

The hip joint in this same series of cadavers was investigated, with attention to changes in its numerous bursae, in the muscles and tendons and in the joint itself. While the hip joint, like the shoulder joint, is an enarthrodial joint, it depends for its stability, unlike the latter, on its

bony architecture and not on its soft tissue structures. It is therefore not remarkable that comparable lesions were infrequently noted.

The great trochanteric bursa, frequently observed to be partitioned by many synovial folds, was occasionally completely divided into an upper and a lower bursa. In 15 cases its walls were thickened and its inner lining frayed and at times partially or completely adherent. The iliopectineal bursa communicated with the joint cavity in 10 per cent of cases, often bilaterally. In 10 instances this bursa was partially or completely obliterated. No changes were observed in the other bursae
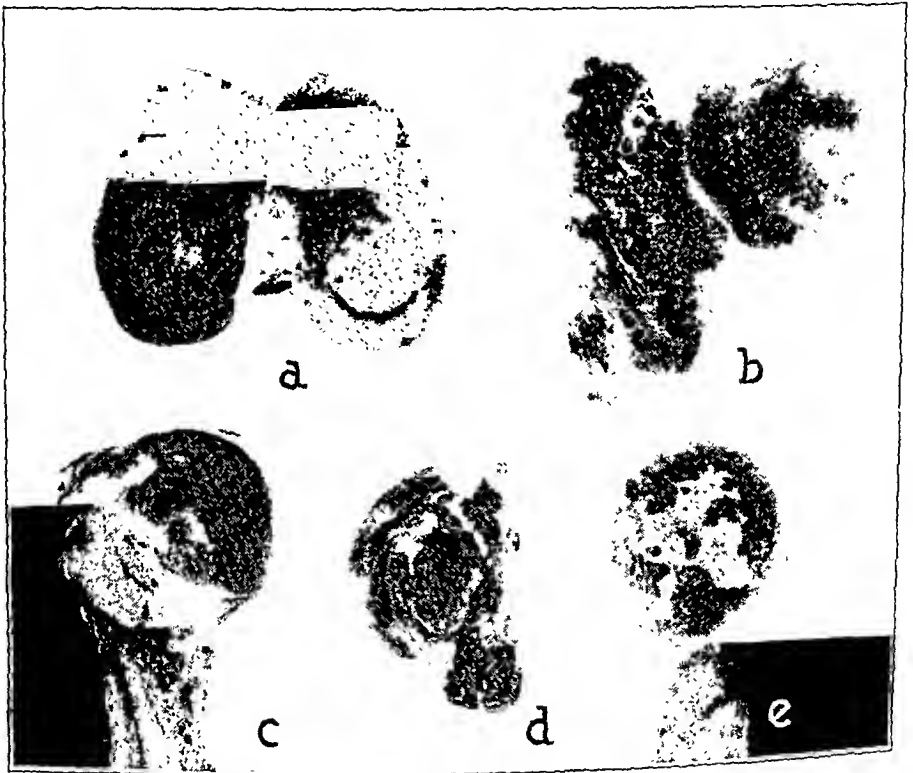
Fig. 6.—Degenerative lesions of the cartilage, with denudation of the underlying bone in areas and secondary eburnation. Hypertrophic changes are present along the margins of the articular surfaces. At *a* is shown the distal articular surface of the femur; at *b*, the head and neck of the femur; at *c, d* and *e*, heads and necks of humeri.

of the hip joint. The relation of infections of the bursa of the great trochanter to the fascial compartments of the thigh has been stressed by Milgram,[23] and the symptom complex of iliopectineal bursitis has been reviewed recently by Finder.[24]

23. Milgram, J. E.: Surgery of Suppuration in the Fascial Spaces of the Thigh. J. A. M. A. **98**:117 (Jan. 9) 1932.

24. Finder, J. G.: Iliopectineal Bursitis, *Arch. Surg.* **36**:519 (March) 1935.

No gross changes were noted in the tendons of the short rotators and abductors which insert about the base of the neck of the femur and merge with the capsule of the hip joint in a manner similar to that of the musculotendinous cuff about the head of the humerus (fig. 2). In only 1 instance, in which there was a comminuted fracture of the
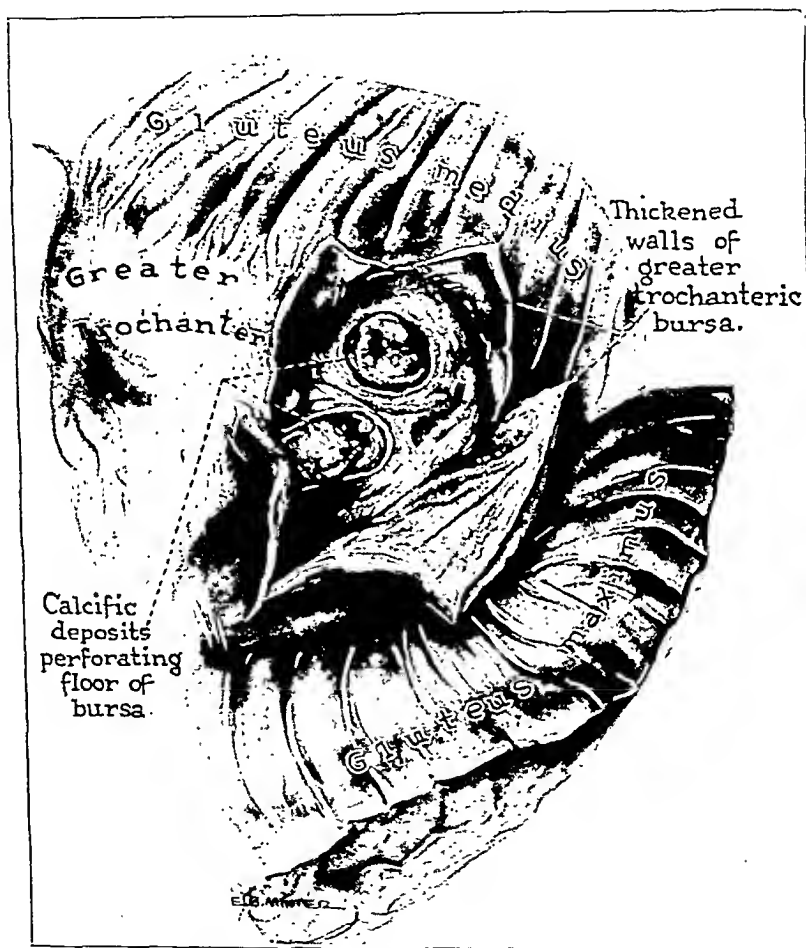
Fig. 7.—Artist's representation of calcific deposits embedded in the floor of a thick-walled great trochanteric bursa in a case of ununited fracture of the base of the neck of the femur.

base of the femoral neck, were advanced changes noted in the floor of the bursa of the great trochanter, two large calcific deposits lying deeply embedded within the fibrillated fibers of the vastus lateralis muscle (fig. 7). The roentgenographic evidence of calcific deposits about the greater trochanter in 30 out of 550 (5.4 per cent) patients aged from

15 to 69, reported by Goldenberg and Leventhal,[25] indicates that slight changes, not grossly evident, might have been revealed by roentgenographic and microscopic studies.

COMMENT

Codman [2] has admitted that since in most of his cases tear of the supraspinatus tendon occurred in aged persons and many of the tears were bilateral, some form of necrosis may have been largely responsible for the lesions and also for their failure to repair. He has been tempted to compromise on the theory that many causes or combinations of causes —age, constitutional factors, calcific deposits within the supraspinatus tendon, or overuse—might result in the same lesion, but he stated that he was convinced that trauma produces the actual rupture in most instances and that the defect should be surgically repaired.

Wilson [19] noted in his cases that, in addition to the actual rupture, degenerative lesions were present in the unruptured portions of the musculotendinous cuff. He stated:

> One cannot avoid the opinion that there are signs of gradual deterioration of the tendon from the excessive use and advancing age with perhaps defective circulation in the background. These changes probably precede and pave the way for rupture of the tendon and this view explains why in many instances rupture finally occurs under conditions that approximate normal use.

There is much evidence to support Meyer's hypothesis of attrition,[26] namely, that in addition to trauma and long-continued friction there is a failure of bodily reparative processes to function adequately. This author has stressed concomitant degenerative lesions in other tissues of the shoulder joint, attritional lesions in other joints of the body, the oval or circular rather than transverse shape of the tendinous defect and the absence of atrophy of the muscle bellies of the completely torn tendons (supraspinatus and long bicipital). He has noted that according to Cronkite and others [27] a supraspinatus tendon ¾ inch (1.9 cm.) wide and 2 mm. thick can bear a pull of 700 pounds and one 3 mm. thick a pull of 1,000 pounds; rupture of a sound supraspinatus tendon which is more than 3 mm. thick is therefore highly improbable. McMaster [28] has demonstrated experimentally that when a sound muscle is subjected to

25. Goldenberg, R. R., and Leventhal, G. S.: Supratrochanteric Calcification, J. Bone & Joint Surg. **18**:205, 1936.

26. Meyer, A. W.: Chronic Functional Lesions of the Shoulder, Arch. Surg. **35**:646 (Oct.) 1937.

27. Cronkite, A. E.: The Tensile Strength of Human Tendons, Anat. Rec. **64**:173, 1936.

28. McMaster, P. E.: Tendon and Muscle Ruptures: Clinical and Experimental Studies on the Causes and Location of Subcutaneous Ruptures, J. Bone & Joint Surg. **15**:705, 1933.

strong traction tears will occur at its origin and insertion and in the muscle belly but not in the tendon itself.

The relation of the anatomic changes produced by degenerative arthritis to advancing age, wear and tear, stress, trauma, occupation, and static deformities has been stressed by Keefer and his co-workers,[29] Meyer [30] and Keyes [31] for human joints, by Bennett and Bauer [32] for bovine joints and by Glauning,[33] Callender and Kelser [34] and others for the articulations of horses.

CONCLUSION

From this evidence I am convinced that the symptom complex of rupture of the supraspinatus tendon represents the effects of trauma, often minimal, on tissues which are the site of degenerative lesions incidental to advancing age, defective circulation, excessive use and attritional changes. The fact that such a lesion is demonstrated at autopsy and in the dissecting laboratory in cases in which there is no history of injury and its high incidence in adult cadavers, especially those of persons advanced in years, indicate that trauma serves merely to hasten the progress of pathologic events already taking place. The wisdom of subjecting a patient with such a condition to surgical procedures is therefore to be questioned.

Defects in the tendons of a patient prior to the fourth decade of life are secondary in most instances to inflammatory processes and calcific deposits, occur less frequently and require relatively severe trauma to further the disruption of the tendon. Surgical repair seems justified in this small group of cases to correct not only the secondary, but also the primary, defect.

Twentieth and Chestnut Streets.

29. Keefer, C. S.; Parker, F., Jr.; Myers, W. K., and Irwin, R. L.: Relationship Between Anatomic Changes in the Knee Joint with Advancing Age and Degenerative Arthritis, Arch. Int. Med. **53**:325 (March) 1934.

30. Meyer, A. W.: Use Destruction in the Human Body, California & West. Med. **47**:375, 1937.

31. Keyes, E. L.: Erosions of the Articular Surfaces of the Knee Joint, J. Bone & Joint Surg. **15**:369, 1933.

32. Bennett, G. A., and Bauer, W.: A Systematic Study of the Degeneration of Articular Cartilage in Bovine Joints, Am. J. Path. **7**:399, 1931.

33. Glauning, W.: Altersveränderungen im Kniegelenk des Pferds, Inaug. Dissert., Regensburg, Josef Habbel, 1936; cited by Meyer.[26]

34. Callender, G. R., and Kelser, R. A.: Degenerative Arthritis: A Comparison of the Pathological Changes in Man and Equines, Am. J. Path. **14**:253, 1938.

RESECTION OF THE CARCINOMATOUS RECTOSIGMOID JUNCTURE

WITH REESTABLISHMENT OF INTESTINAL CONTINUITY: PRELIMINARY REPORT

HUBERT R. ARNOLD, M.D.

SAN FRANCISCO

The rectosigmoid, or retrosigmoid juncture, is that part of the bowel opposite the reflection of the peritoneum in the lowermost portion of the pelvic cavity. Clinically the terminal inch (2.5 cm.) of the sigmoid flexure of the colon and the uppermost inch of the rectum are considered as composing it. Next to the stomach the rectum is the most common site of malignant disease of the gastrointestinal tract. It is generally accepted that rectal carcinomas make up about 4 per cent of all carcinomas and that about 80 per cent of intestinal carcinomas appear in the rectum. Rankin and his associates [1] stated:

> We believe that most carcinomas of the rectum are at the rectosigmoid juncture, that the next point of frequency is in the ampulla of the rectum, and that the site of least frequency is the anal canal and the lower five or six cm. of the rectum.

One is impressed with the high incidence of carcinoma involving this portion of the bowel. It follows that a surgeon who makes a permanent abdominal colostomy opening with removal of the lower part of the bowel for carcinoma of the lower portion of the sigmoid flexure and the rectum does so in most instances for carcinoma of the rectosigmoid juncture. If a satisfactory operation could be devised for removal of the carcinomatous rectosigmoid and reestablishment of the continuity of the bowel, leaving the patient with a normal anus, it would be a great boon to that unfortunate group who heretofore have been left with an abdominal anus after the removal of the rectosigmoid for malignant disease.

I have developed and used such an operation and believe others can apply it successfully in selected cases of carcinoma of the rectosigmoid. The technic involved is not new but is a combination of well known procedures, the rectosigmoid being resected in a one stage abdominosacral operation and continuity of the sigmoid flexure and the rectum being reestablished (by means of the Mikulicz technic)

1. Rankin, F. W.; Bargen, J. A., and Buie, L. A.: The Colon, Rectum and Anus, Philadelphia, W. B. Saunders Company, 1932.

immediately below the sacrum. Crushing clamps are left on the proximal and distal ends of the bowel, to be removed in about forty-eight hours, after which, a few days later, right angle clamps are applied to cut through the septum.

OPERATION

The abdomen is opened by a paramedian incision on the right, extending from the symphysis pubis to about 1 inch (2.5 cm.) above the umbilicus. A self-retaining retractor is adjusted, and the abdomen is explored to determine operability. All of the bowel except the descend-

Fig. 1.—Abdomen held open by a circular retractor, the viscera being held in the upper part of the abdomen by self-retaining visceral retraction. An oval rent has been made in the mesosigmoid, extending down toward the pelvis. The superior hemorrhoidal artery has been ligated above the "critical point." The mesial and lateral peritoneal incisions are shown.

ing colon is placed in the upper part of the abdomen and held there by packs. I have devised a special circular retractor (fig. 1) which permits self-retaining visceral retraction as well as parietal retraction. The lower portion of the sigmoid flexure is pulled up, the mesosigmoid being spread into the shape of a fan. The superior hemorrhoidal and the sigmoid artery are identified. The peritoneum of the mesosigmoid is opened mesially about opposite the bifurcation of the aorta. The

superior hemorrhoidal artery is doubly ligated and is severed between ligatures proximal to its branching to form a part of the marginal artery (fig. 1). The opening in the mesosigmoid is continued through to the lateral side. By enlargement of this rent downward the pelvic portion of the colon is mobilized, but the blood supply is not materially affected, because the continuity of the marginal artery is not interrupted. A wedge-shaped piece of the node-bearing mesosigmoid is removed with the distal portion of the sigmoid flexure. An incision is made in the peritoneum of the mesentery on the mesial side of the pelvic portion of the colon and is carried down to the bladder. A similar incision is
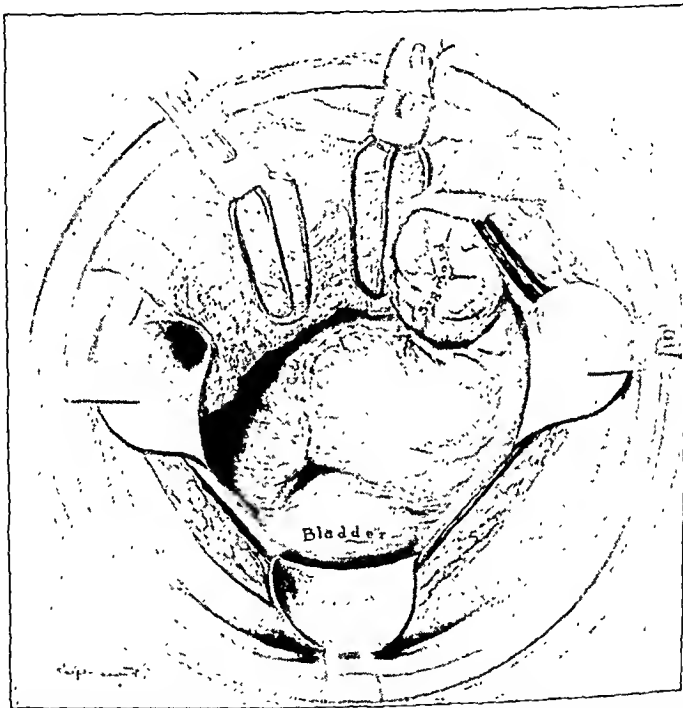
Fig. 2.—Abdomen held open by a retractor. The pelvic floor has been reestablished.

made on the left side of the bowel and is carried down to the reflection of the peritoneum at the base of the pelvic cavity. The left ureter comes into view. The lower ends of the incisions are connected by a transverse incision through the peritoneum. The edges of the peritoneum so incised are dissected free, and the peritoneal bands holding the bowel to the bladder are severed with scissors. The bowel is freed anteriorly down as far as possible into the pelvis. The distal portion of the sigmoid flexure is now lifted up, and a hand is inserted posterior to it, freeing it from the sacrum down to the coccyx. The terminal

portion of the sigmoid flexure and the rectosigmoid are now pushed down into the pelvis, and a new, high pelvic floor (fig. 2) is established by approximation of the lateral peritoneal flaps and suturing of their upper ends across the anterior portion of the sigmoid flexure to its anterior peritoneal covering. Thus the peritoneal cavity is entirely closed. The descent of the distal portion of the sigmoid flexure is made possible by the severance .of the superior hemorrhoidal artery and the rent made in the mesosigmoid. The abdomen is closed in the usual way, and the patient is placed on his right side. The sacrum and the perineal region are prepared; the anus is closed with a purse
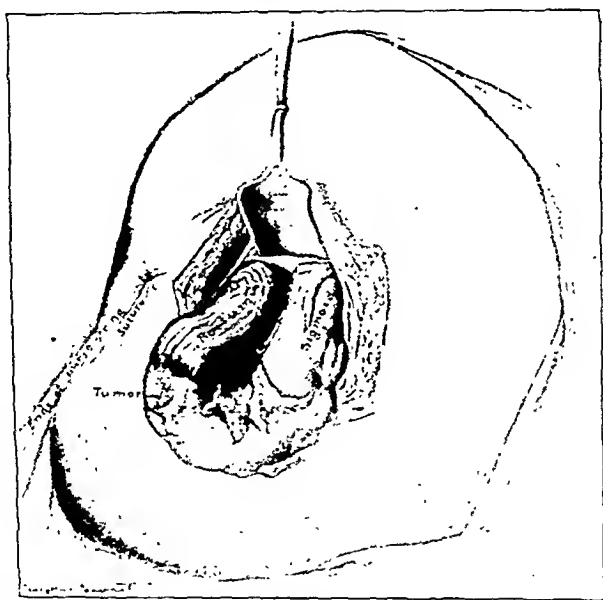
Fig. 3.—Patient in the right lateral position. (The left lateral position may be used.) The purse string suture on the anus and the T-shaped sacral incision can be seen. The rectosigmoid has been pulled through the incision. The limbs of the bowel have been sutured as with the Mikulicz procedure. The coccyx has been removed.

string suture, and an incision is made in the midsacral line from a point 1 inch above the anus to the sacrococcygeal articulation. At this point a transverse incision is made, forming a T-shaped incision. These incisions are carried deeper, and the coccyx is disarticulated. The posterior aspect of the bowel is exposed. The fascia propria is divided opposite the sacrococcygeal articulation, and the bowel is dissected free from the sacrum. The middle sacral artery may require ligatures. The rectosigmoid is dissected free from its lateral attachments and

anteriorly until a finger can be inserted around the bowel below the
tumor. An ordinary hernia tape is inserted around the bowel and used
for traction. The rectosigmoid is mobilized up to the pelvic floor.
The rent in the mesosigmoid now comes into view, and the peritoneal
covering of the distal portion of the sigmoid flexure is seen. The loose
perirectosigmoidal tissues and node-bearing glands are dissected out.
The rectosigmoid is now pulled out through the sacral incision (fig. 3);
several nonpenetrating sutures are used to unite the serosae of the
limbs of the intestinal loop on either side, and two crushing clamps are
placed on the bowel at a safe distance from the growth, above and
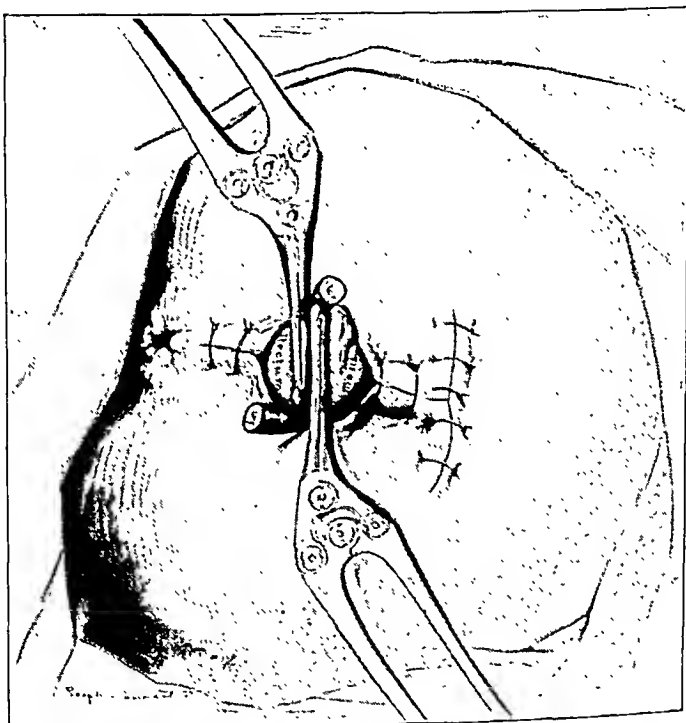
Fig. 4.—Crushing clamps in place. A segment of bowel has been removed.
The T-shaped incision has been sutured. The purse string suture has been
removed from the anus. Small cigaret drains have been placed on either side of
the bowel. (Straight Kocher forceps may be used instead of heavy crushing
clamps, since they are more easily taped to the buttocks. Instead of using forceps
one may tie the ends of bowel with braided silk ligatures.)

below the rectosigmoid. The bowel is severed with a cautery both
distally and proximally between these clamps (fig. 4), the rectosigmoid
being thus removed with the tumor within it. A small rubber drain is
inserted on either side of the ends of bowel, and the tissues are loosely
approximated around the ends of bowel and the drains. The anal purse
string suture is removed. The crushing clamps are left in place for

forty-eight hours, after which they are removed, and a few days later the right angle clamps (fig. 5) are placed in the usual way to cut through the septum separating the intestinal lumens. These slough out a few days later, and the sacral wound granulates in, the continuity of the bowel being reestablished. As an alternative, the loop of bowel containing the carcinoma may be left protruding through the sacral incision and may be severed between clamps at a later date; this gives the sacral wound time to heal partially before it is contaminated with fecal material. A piece of rubber dam is thrust up between the mobilized terminal portion of the sigmoid flexure and the sacrum and is left protruding through the sacral incision for drainage.
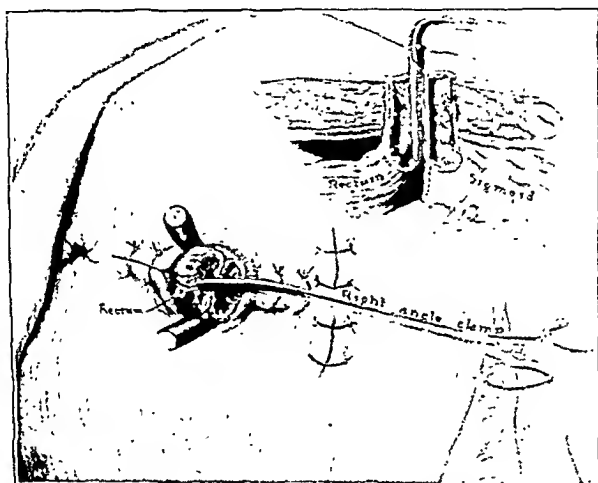
Fig. 5.—Right angle crushing clamp on the intestinal septum. The insert is a side view of the clamp in place, with part of the bowel cut away. If one desires to remove a larger segment of the intestinal septum two clamps may be used, placed about ½ inch (1.2 cm.) apart.

REPORT OF A CASE

I have performed this operation in only 1 case, with the following result:

A man aged 59 had well advanced annular adenocarcinoma of the rectosigmoid. He was in good physical condition. The blood pressure was normal. All the organs were normal on routine examination. Routine laboratory examination showed nothing of note. The rectosigmoid was not particularly fixed. The abdomen was opened, and no evidence of metastasis was found. The operation was performed as has been outlined. The patient rallied normally from the operation. Forty-eight hours later the two colostomy clamps were removed, and immediately the two right angle crushing clamps were applied. On the third day fecal material came through the proximal colostomy opening, and on the fourth day the patient was passing gas. The ends of the bowel showed good color. The sacral wound continued to look healthy, and the right angle clamps came off a few

days later. On the eighth day the sacral wound was only about the size of a half-dollar. A rectal tube was inserted through the anus, well up above the sacral opening and into the sigmoid flexure. This part of the operation was satisfactory. On the third, fourth and fifth days there was some abdominal distention, which subsided on the fifth day and did not return. The abdomen thereafter showed nothing of note. On the fourth day an infection of the thorax developed, which gradually became worse. There was a large amount of mucus, and considerable dyspnea was noted. A roentgenogram of the chest on the eighth postoperative day showed the lungs infiltrated with numerous minute round opaque areas. There was some roentgen evidence of edema. The left side of the heart was hypertrophied. The patient died of the thoracic infection on the ninth postoperative day, but the result of the operation had been normal. It is a matter of conjecture whether this patient's life would have been saved by a multiple stage operation.

Autopsy.—Autopsy failed to show any evidence of metastasis in the abdominal cavity. The liver, spleen, kidneys and mesentery were normal. There was no evidence of peritonitis. All the peritoneal suture lines were in good condition. There was no evidence of obstruction in the descending colon, and the color of the sigmoid flexure was normal down to the colostomy opening. No part of the operative area showed the least evidence of a flaw. The heart was somewhat hypertrophied; the lungs were edematous, and the lower lobe of the right lung was collapsed. The lungs showed pneumoconiosis throughout, and microscopic sections showed widespread bronchopneumonia.

COMMENT

By the usual sacral resection of the rectosigmoid it is extremely difficult and sometimes impossible to pull enough of the terminal portion of the sigmoid flexure down to resect satisfactorily the rectosigmoid and reestablish intestinal continuity. By mobilizing the terminal portion of the sigmoid flexure and the rectosigmoid by the abdominal approach it is usually possible to accomplish this, especially when the Mikulicz technic is used in so doing, since less bowel is needed for this purpose than when an end to end anastomosis is undertaken in such a small space. For an end to end anastomosis the bowel must be delivered through the incision. This necessitates access to a considerable length of bowel, which is not necessary for the Mikulicz anastomosis. By the Mikulicz principle a wider resection of the diseased bowel is possible. Suturing the bowel at this site is unsatisfactory, there being a tendency to nonunion and later to stricture formation.

This operation can justly be objected to on the ground that a sufficient portion of the mesosigmoid is not removed. In a given case one may decide at the operating table, with the patient's abdomen open, that a larger part of the mesosigmoid should be removed and may proceed with one of the conventional types of abdominoperineal operation followed by permanent abdominal colostomy. In a case in which the pelvic portion of the colon cannot be sufficiently freed to permit the procedure outlined one makes any one of the permanent types of colostomy opening. In all instances in which the procedure outlined

can be followed it is possible to clear away the node-bearing tissues around the prostate gland and the seminal vesicles or those on the posterior vaginal wall, the cervix and broad ligament. On the other hand, with such a procedure one must risk involvement of the anal and perianal tissues in the spread of the carcinoma. If, however, it is decided beforehand that the growth encroaches too much on the tissues surrounding the anus or if the anal area is involved in the growth or its metastases, naturally permanent colostomy is done, with the removal of all the lower portion of the bowel and the anus, unless one cares to establish a sacral anus. With my operation, abdominosacral resection of the rectosigmoid with the Mikulicz principle of anastomosis through the sacral incision, there is almost no chance of peritonitis, since the bowel is not opened in the abdominal cavity. The sacrum is peculiarly immune to infection. If the operative risk is poor the sacral resection can be left for a later date, since the circulation to this portion of the bowel is not materially interrupted. If one chooses to delay sacral resection, a rubber dam is tucked well down to the coccyx between the sacrum and the mobilized distal portion of the sigmoid flexure and the rectosigmoid, and at the close of the operation a corner of the dam is drawn out through an incision made alongside the coccyx for drainage, as described by Smith.[2] If resection of the exteriorized rectosigmoid is left for a still later date the procedure becomes a three stage operation.

Babcock[3] has devised an operative treatment for resection of the carcinomatous rectosigmoid in which he eliminates the abdominal colostomy, substituting formation of a sacral anus. He has claimed good functional results by this method owing to improvement in the technic and in the viability of the bowel used. He has stated that in the earlier attempts at formation of a sacral anus the end of the sigmoid flexure brought to the perineum sloughed for some distance into the pelvic cavity and left a cicatricial opening that was the source of much later trouble. By his method, with the preservation of the blood supply of the segment of sigmoid flexure brought through the perineum, necrosis of the bowel does not occur, and with an ample opening there is little chance for stricture, so that the bowel empties completely. In some instances he has attempted to obtain a measure of intestinal control by a secondary plastic operation on the sacral anus. In other cases, at a second operation he has split the anal ring anteroposteriorly, dissected away the mucosa, freed the sigmoid-sacral anus and pulled

2. Smith, D.: Two-Stage Procedures in Abdominoperineal Resection of the Sigmoid and Rectum for Cancer, Tr. Am. Proct. Soc. **33**:103, 1932.

3. Babcock, W. W.: The Operative Treatment of Carcinoma of the Rectosigmoid with Methods for the Elimination of Colostomy, Surg., Gynec. & Obst. **55**: 627 (Nov.) 1932.

it down through the sphincters to reestablish a normal anus. This is essentially the Hochenegg technic. In some instances the intestinal lumens have been connected by removal of the intervening tissues at a later operation. In the abdominal part of the operation Babcock does a wide dissection, ligating the sigmoid and the superior hemorrhoidal artery, dividing the mesosigmoid high in its course, and removing all the peritoneum from the bifurcation of the common iliac arteries down to the bottom of the pelvic cavity. He makes no attempt to peritonealize this large denuded area or to form a new pelvic floor. Owing to the ligation of the blood supply to the lower portion of the sigmoid flexure and the high division of the mesosigmoid, it is necessary to pull a large part of the sigmoid flexure down through the sacral incision and amputate it at a high point. This is not always possible or desirable, since in many cases carcinoma of the rectosigmoid remains strictly localized for some time, and wide dissection of tissues is not necessary. On the other hand, a sacral colostomy opening is not as desirable as the normal anus. When the carcinoma involves the anus and surrounding tissues or the portion of the rectum which is below the rectosigmoid, I believe Babcock's method is preferable to permanent abdominal colostomy if good functional results can be obtained. However, in such a case a less extensive abdominal dissection and the establishing of a new pelvic floor with a permanent colostomy opening might be a better procedure. Alternatively, Babcock's extensive abdominal dissection could be combined with the Mikulicz type of anastomosis through the sacral incision.

The old Kraske operation is familiar to all surgeons. It includes removal of a portion of the sacrum, mobilization and amputation of the rectum and the rectosigmoid juncture and formation of a sacral anus or end to end anastomosis. Kraske also devised, later, a combined abdominoperineal operation, freeing the rectum and the sigmoid flexure from above and following this procedure with sacral amputation of the bowel. Quénu and others quickly saw the merit of this method and became ardent advocates of the combined procedure. In a few instances the carcinomatous bowel has been resected and anastomosis done, the anus being left intact. The terminal opening in the sigmoid flexure has been disposed of in a variety of ways by different surgeons.

There are numerous combined abdominoperineal methods for resection of the lower portion of the sigmoid flexure, the rectosigmoid and the rectum, with permanent abdominal colostomy; these include the methods of Miles, Coffey, Lahey, Jones, Rankin and many others.

With the method described by me a cecostomy could be done prior to or coincidentally with the abdominal part of the operation. This would prevent early soiling of the sacral field.

Any surgeon treating carcinoma of the rectosigmoid should have at his disposal many different operative procedures. No one method can be used to the exclusion of all others, since patients present themselves in varying stages of the disease. The two extremes, the abdomino-perineal route and the perineal route alone, are represented by the work of Miles, who uses the abdominoperineal route almost to the exclusion of all others, claiming a high percentage of recurrence with the perineal route alone, and by the work of Lockhart-Mummery, who has abandoned all methods except the perineal one, claiming that the difference in recurrence of the growth with the two methods is negligible and that practically as much tissue can be removed by the perineal as by the abdominoperineal route.

My method is also applicable in cases of tumor of the lower portion of the sigmoid flexure in an early stage and too low to be resected from above with anastomosis of the bowel. It can be applied to any operable benign lesion of the lower portion of the sigmoid, the recto-sigmoid and the upper part of the rectal ampulla, provided of course, too short a mesosigmoid does not preclude proper mobilization of the bowel.

I believe that the peace of mind of the patient is as important in many instances as his health or even his life. I believe that few, if any, more patients would die after the use of my method than after the use of the abdominoperineal method with removal of a larger portion of the mesosigmoid and permanent abdominal colostomy. Any disadvantage the method may have is overshadowed by the great advantage of a naturally situated anus.

CONCLUSION

A method is described for resection of the carcinomatous recto-sigmoid by a combined abdominosacral technic, the Mikulicz procedure being used to reestablish the continuity of the bowel through the sacral incision.

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CARCINOMA OF THE LIP

CLINICAL AND PATHOLOGIC STUDY OF THREE HUNDRED AND NINETY CASES, WITH REPORT OF FIVE YEAR CURES

EDWARD T. NEWELL Jr., M.D.[*]

BALTIMORE

There have been many studies and reports on carcinoma of the lip since the publication of the paper of Broders[1] in 1920 on the grading of tumors. However, on reviewing the more recent literature, one finds little accord among surgeons, radiologists · and dermatologists on the methods and results of treatment. This may be because both operation and irradiation are satisfactory methods of treatment provided sufficient skill and knowledge are used. The purpose of this paper is to report a rather large series of cases followed beyond the five year period, in which the tumors were treated by surgical operation, and to emphasize the necessity for routine microscopic examination. A comparison is made with the other accepted forms of treatment, that is, irradiation and cauterization. It is difficult to make a true comparison of results, however, because of differences in duration, severity and size of the lesions reported in the literature and the varying periods during which the cases have been followed.

Five year follow-ups have been used as the best index to the results of treatment. The disadvantage of selecting a shorter period has been well borne out in this study, for a number of patients have shown recurrence or metastasis two to four years after treatment, and several four to seven years later. One patient had a recurrence twenty years later. This is contrary to the opinion of Kelly,[2] MacMahon[3] and others, who concluded that recurrence after two years is almost nil in cases of carcinoma of the lip.

The 390 cases forming the basis of this study were obtained from the records of the surgical pathologic laboratory of the Johns Hopkins

1. Broders, A. C.: Squamous Cell Epithelioma of the Lip, J. A. M. A. **74:** 656 (March 6) 1920.

2. Kelly, E.: Radium Therapy in Carcinoma of the Lip, J. A. M. A. **100:** 388 (Feb. 11) 1933.

3. MacMahon, J. S.: Squamous Cell Carcinoma of the Lip, Australian & New Zealand J. Surg. **7:**40 (July) 1937.

Hospital from 1900 to 1933. The diagnosis of carcinoma has been made in every instance from the sections, except in 10 of the earlier cases (all cases of hopeless cancer). This is likewise true of the cases in which metastasis occurred. The lesions dealt with in this report were, in general, fairly well advanced. Besides affecting the percentage of five year cures unfavorably, the delay in treatment shows the need for more prompt attention to lesions of the lip. The percentage of patients who showed metastasis or recurrence on first examination (36.4 per cent, or 143 of 390 patients) indicates the delay in diagnosis and treatment. The average duration of symptoms was in excess of two years. Kennedy,[4] from New York, reported 33 per cent with metastasis among the 98 patients on whom dissection of the cervical glands was done, while clinically 60 per cent of the patients had palpable glands. Broders at the Mayo Clinic found metastasis in 24 per cent of the patients on whom dissection of the cervical glands was done. Kelly, of Baltimore, however, in his series of 252 cases found that only 14 per cent of patients had palpable cervical glands on admission. He also reported another group, representing 20 per cent of his series, who previously had been treated by operation or irradiation elsewhere, but the incidence of metastasis in this group is not stated. MacMahon, from the Royal Prince Albert Hospital in Sydney, Australia, reported 10.3 per cent of patients with cervical metastases in 299 cases in which dissection of the cervical glands was performed.

CLINICAL FEATURES

The lesion first noticed by most of the patients was a small, painless ulcer, which at first grew slowly. Scabs often formed, and the lesion sometimes healed before a raw area reappeared. Frequently the patients stated that they had had fever blisters before, but that this time the fever blister did not heal. The lesions usually became worse after the use of salves and mild caustics, although there was seldom any associated pain. Other early lesions noted by the patients were warts, cracks, fissures, leukoplakia and chapping of the lips.

In regard to the etiologic factors, an attempt was made to note the relation of carcinoma of the lip to smoking, poor oral hygiene and exposure to the wind and sun. No satisfactory statistical evidence was found, but it seems evident, as emphasized by Bloodgood[5] and others, that chronic irritation in the form of the factors mentioned plays a definite

4. Kennedy, R. H.: Epithelioma of the Lip with Particular Reference to Lymph Node Metastases, Ann. Surg. **99**:81 (Jan.) 1934.

5. Bloodgood, J. C.: Lesions of the Oral Cavity and of the Jaws, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1930, vol. 4, chap. 4.

Fig. 1.—Photograph of a man aged 51 with a typical squamous cell carcinoma of the upper lip of three months' duration. A V excision of the lip was done. The patient was well seven years later. There was no recurrence.
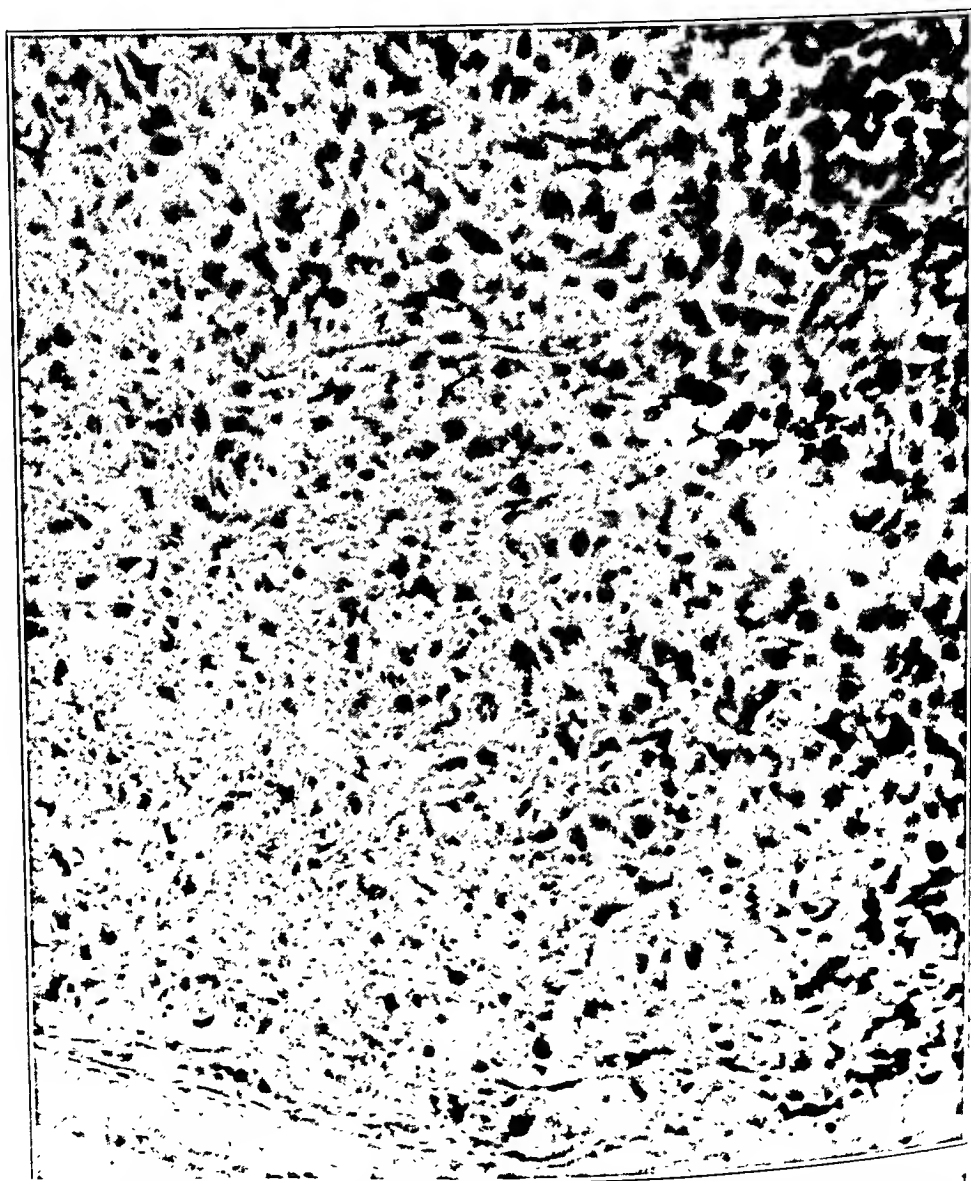
Fig. 2.—Low power photomicrograph of the lesion illustrated in figure 1. Notice the lack of pearl formation and the invasive character of the squamous cells.

part, although it is by no means the sole cause. A study of the occupations of the patients showed the greatest number to be farmers. The hygienic condition of the mouth was poor in the vast majority of cases, many patients having a positive test for the organisms of Vincent's angina. Dirty, ragged, tobacco-stained teeth were noted frequently. In 2 cases carcinoma of the lower lip developed at the site of trauma from a ragged upper tooth.

TABLE 1.—*Age Incidence of Carcinoma of the Lip*

	Age, Years						
	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Lower lip							
Squamous cell carcinoma.................	3	25	50	74	65	31	4
Malignant warts (papillary carcinoma grade)	0	3	9	10	11	7	1
Basal cell carcinoma......................	0	0	2	2	2	1	0
Upper lip							
Squamous cell carcinoma.................	0	2	1	4	5	1	0
Basal cell carcinoma..................	0	2	4	10	10	3	0
Adenocarcinoma	0	0	0	1	1	0	0

TABLE 2.—*Statistics on Carcinoma of the Lip*

	Number of Cases	Sex of Patients		Average Age, Years	Average Duration of Lesion, Months	Condition on Admission		
		Males	Females			No Metastasis	Metastasis	Recurrences
Lower lip								
Squamous cell carcinoma (grade 2, 3 and 4)......................	281	276	5	55.9	28.1	151	103	27
Malignant wart (papillary carcinoma)	47	46	1	57.1	30.8	47	0	0
Basal cell carcinoma (all grades)	8	8	0	57.2	46.1	8	0	0
Upper lip								
Squamous cell carcinoma (all grades)	16	12	4	54	20	12	1	3
Basal cell carcinoma (all grades)	36	23	13	57	28	27	0	9
Adenocarcinoma (all grades)......	2	2	0	60	3	2	0	0

Tables 1 and 2 summarize some of the important statistics on carcinoma of the lower and upper lips, based on the cases studied. The age incidence agrees well with that of other published reports. The duration of the lesion before examination varies considerably. The average time in this series is a little over two years. This gives a somewhat false impression, because it also includes the patients who have been treated previously by improper methods. In many instances, when the patient stated that the lesion had been present five, ten or fifteen years. it was found that actually a benign lesion had been present during

this period, and on careful questioning the patient admitted that there had been very little, if any, growth during this time and that only in the past few months (not more than twelve) had growth and destruction really occurred.

The relation to sex and race is interesting, although the latter is not adequately represented because of the large number of Bloodgood's private patients included in this series. Less than 1.5 per cent of the 390 patients were Negroes. Only 1.8 per cent of carcinomas of the lower lip occurred in women, while for carcinoma of the upper lip the percentage was much higher, 45.9 per cent of these lesions occurring in women.

Mention has already been made of the number of cases in which metastasis occurred. Of the total number of 390 cases, 143 presented metastasis, recurrence or both on the patients' first admission to the hospital, as shown by microscopic examination. In table 2, under the heading "Metastasis" are included both lesions with metastasis and lesions with recurrence plus metastasis. In the group under the heading "Recurrences," only recurrent lesions are included in which there were no metastases on first admission. A discussion of cases in which the lesions were arrested beyond the five year period will be presented later, when treatment is considered. No mention has been made of the size of the tumor, although it is evident that this is an important consideration. The various descriptions as to the size were usually estimations, so that no statistical report of the size of the lesions could be made.

PATHOLOGIC PICTURE

In the series of 390 cases, there were 344 cases of squamous cell carcinoma, 44 cases of basal cell carcinoma and 2 cases of adenocarcinoma. The incidence of basal cell carcinoma of the lower lip is 2.1 per cent and that of basal cell carcinoma of the upper lip is 66.6 per cent. The incidence of basal cell carcinoma of the lower lip is probably lower than this, as this includes basal cell lesions which involved the lip at the time of examination but which the patient thought had begun just below the vermilion border. Among lesions of the upper lip, carcinoma on the cutaneous side of the upper lip was included.

The term "malignant wart" has been used to indicate the low grade papillary type of squamous cell carcinoma, and such a growth is equivalent to a grade 1 carcinoma of Broders' classification. This is the classification previously adopted by Bloodgood. No attempt has been made to reclassify the cases according to Broders' method of grading, although after a study of the sections in this series it is evident that the degree of microscopic differentiation is of value both in the selection of treatment and in prognosis, when used in conjunction with the dura-

tion and extent of the disease, as MacCarty and Broders recommended. Determination of the type of carcinoma (whether basal cell or squamous cell) is of great value, as is well known, in prognosis. There was no case of basal cell metastasis in this series, although recurrences did take place.

There are recorded in the surgical pathologic laboratory a number of benign lesions of the lip which were clinically diagnosed as malignant and a number of early malignant lesions in which the clinical impression was that of a benign lesion. This is ample evidence that a microscopic study should be made of all questionable lesions of the lip for which carcinoma is considered a possible diagnosis. In figures 3, 4 and 5 are shown three lesions of the lip. The lesions in figures 3 and 4 were carcinomas, and that in figure 5 was a benign wart. These three pictures were shown to four clinicians, who were requested to state which lesions they thought were malignant. In every instance the lesion in figure 5 was pointed out as a malignant instead of a benign lesion and that in figure 4 as a benign instead of a malignant lesion.

This emphasis on microscopic examination for carcinoma of the lip has also been made by many other authors, among whom are Hyndman,[6] Kennedy,[4] Martin,[7] Figi [8] and Richards.[9] Hyndman in particular stated that the microscopic appearance is of great value in determining the necessity of removing or irradiating the cervical glands. This is also the tendency at the Mayo Clinic, where dissections of the neck are done routinely for grade 2, 3 and 4 carcinoma of the lip (Claude F. Dixon).[10] At the Johns Hopkins Hospital, irradiation and surgical treatment are now both used, but when surgical treatment is used and the microscopic picture is that of a malignant wart (grade 1 carcinoma, Broders) the cervical glands are not removed.

RESULTS OF TREATMENT

During the period under consideration, 390 patients sought treatment. Of that number, 349 were given surgical treatment; 24 presented hopeless lesions and were treated with palliative measures; in 13 there

6. Hyndman, O. R.: Carcinoma of the Lip with a Clinicopathological Analysis of Seventy-Seven Cases, Arch. Surg. **27**:250 (Aug.) 1933.

7. Martin, H. E.: Treatment of Cancer of the Lip, Am. J. Surg. **30**:215 (Nov.) 1935.

8. Figi, F. A.: Epithelioma of the Lower Lip, Surg., Gynec. & Obst. **59**: 810 (Nov.) 1934.

9. Richards, G. E.: Radiological Treatment of Cancer of the Lip, Canad. M. A. J. **35**:490 (Nov.) 1936.

10. Dixon, C. F.: Submental and Bilateral Submaxillary Dissection, S. Clin. North America **15**:1303 (Oct.) 1935.

Fig. 3.—Photograph of a man aged 56 with a squamous cell carcinoma of six months' duration. A V excision of the lip was done. The patient died two years later of angina pectoris. There had been no recurrence of the carcinoma.

Fig. 4.—Photograph of a man aged 46 who had carcinoma of the lip of three months' duration. The clinical impression was benign tumor. A V excision of the lip was done. There was local recurrence eight years later of a similar low grade squamous cell carcinoma.

Fig. 5.—Photograph of a man aged 66, with a benign squamous cell wart of one year's duration. The clinical impression was malignant wart. A V excision of the lip was done. The patient was well three years later. There was no ·rrence.

were insufficient data for classification, and 4 patients with early carci-
noma received primary irradiation treatment. The total number of
patients followed over a period of five years or more was 328. Of that
number, 181 lived for a period of five years, 114 died from carcinoma
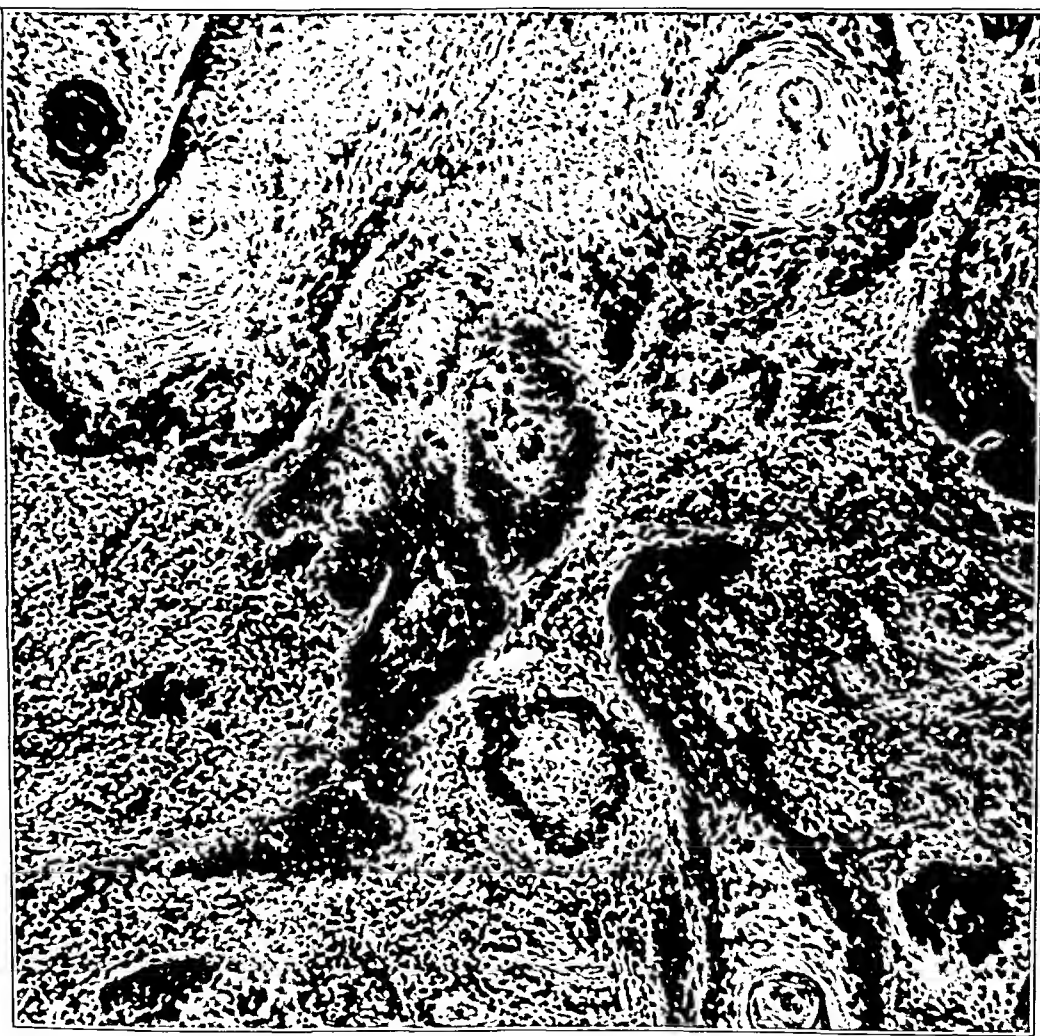
Fig. 6.—Low power photomicrograph of the lesion shown in figure 3. Note
the invasive character of the epithelial cells at the base of the ulcer and the
tendency to pearl formation.

and 34 died of some intercurrent disease within the five years and are
excluded from all statistics. Thus, the percentage of five year cures
for the 328 patients (including patients with hopeless cancer) is 61.6
per cent.

The cases have been divided into as few groups as possible, so that a sufficient number will have been followed in each group to make the statistics as accurate as possible. In table 3 the cases have been divided into three groups, according to treatment received. Group 1 consists of 176 cases in which there was no evidence of metastases clinically and in which only excision of the tumor of the lip was done. After the 17

Fig. 7.—Low power photomicrograph of lesion seen in figure 4. Note the carcinoma beginning at the base of the lesion. This is illustrated better in a high power photomicrograph.

cases in which the patients died of some intercurrent condition were deducted, the percentage of five year cures in the 149 cases traced was 80.9. Group 2 consists of 90 cases in which the tumor was excised, dissection of the cervical glands performed and no metastasis found. Of this group 85.3 per cent of the 80 patients traced were well after five years. At first glance one might conclude that the method employed

for group 2 is the best procedure to follow in the treatment of cancer of the lip in the early stages, but it must be remembered that the two groups are not identical. It is possible that in 2 or 3 cases in group 1 metastasis may have been present when the tumor was excised. Also 1 case is included in group 1 in which dissection of the glands of the neck was advised but permission was refused, and metastasis and death occurred.
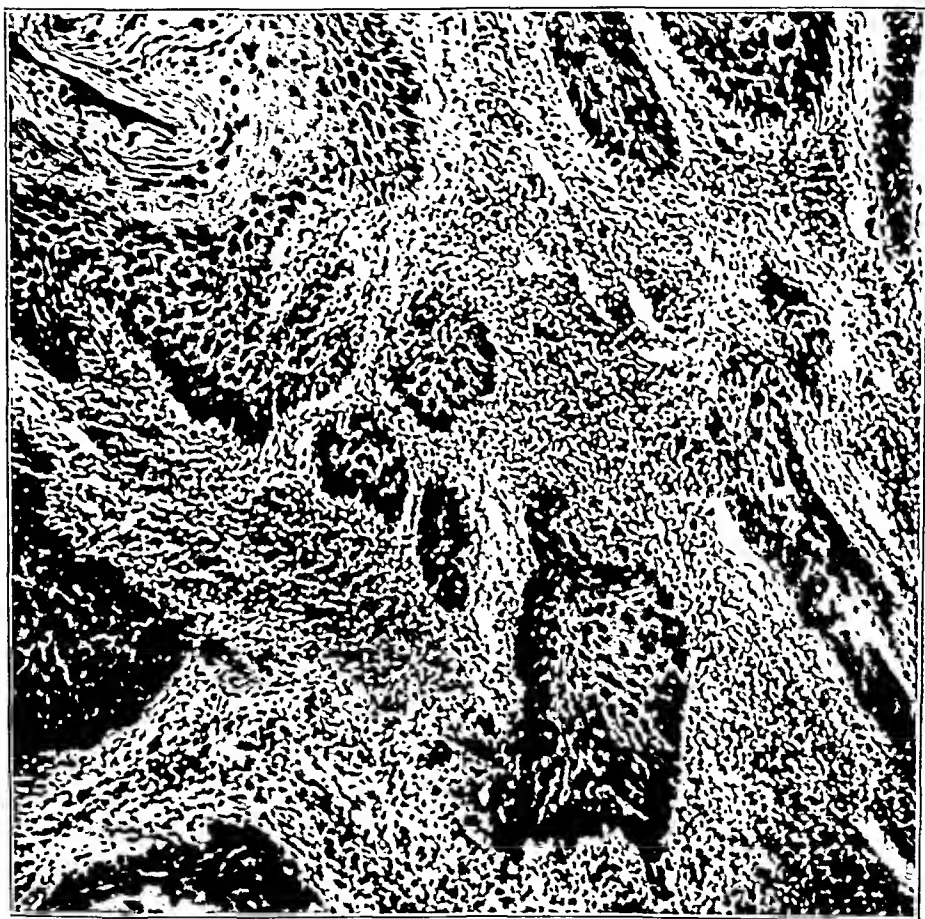
Fig. 8.—Low power photomicrograph of the recurrent lesion shown in figure 4 and figure 7.

However, even with this slight inequality in comparison, the patients in the cases of group 2 were, by and large, "poorer risks" than those in group 1, so that dissection of the cervical glands in certain selected cases seems to be the best procedure. Just what the criterion should be it is difficult to state, but for patients with clinically palpable glands or with

a highly invasive type of carcinoma (grade 3 or 4) it would seem advisable to perform dissection of the cervical nodes.

Group 3 consists of 83 cases in which metastases were found. In this group radical excisions, including cervical dissections and plastic

Fig. 9.—Low power photomicrograph of the benign wart shown in figure 5. The basement membrane is intact, and there is marked leukocytic infiltration. However, there is no change in the size or character of the epithelial cells.

repair when necessary, were performed. The operative mortality was chiefly in this series, 8 of the 13 operative deaths occurring in group 3 and 4 in group 2. An additional operative death was that of a patient

excluded from classification because of insufficient data. The percentage of five year cures in this group is low, 22.5. This emphasizes again the importance of early treatment of carcinoma of the lip.

One of the first impressions formed in this study was the large number of patients who had been previously treated with caustics, roentgen therapy or radium therapy. There were 66 such patients with involvement of the lower lip in this study, and 55 of the 66 presented metastasis or extensive recurrence on first admission. This is not an attempt to point out the inefficiency of irradiation, but to bring out the
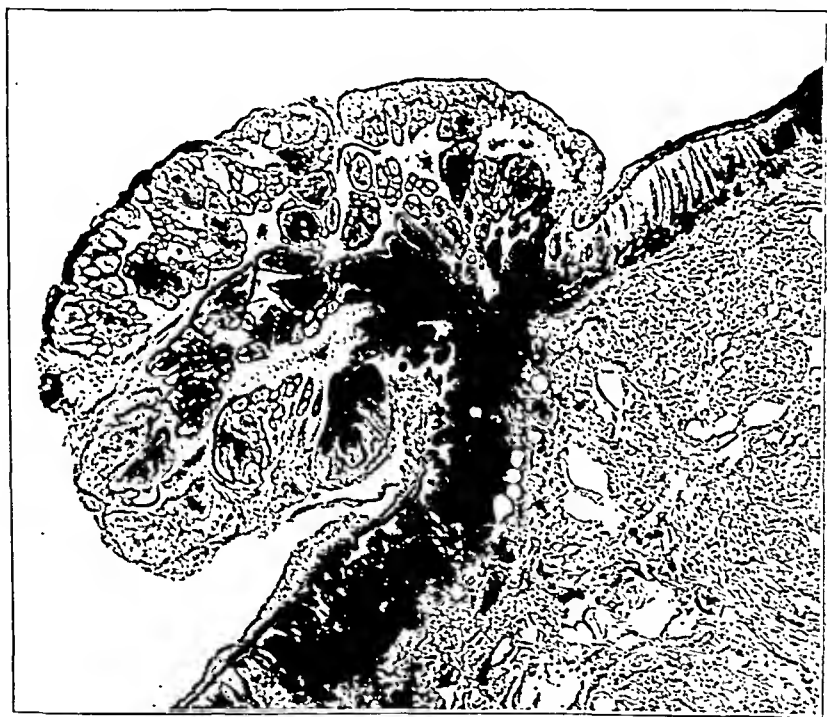
Fig. 10.—Very low power photomicrograph of the benign lesion shown in figures 5 and 9. This shows very well the character of the entire wart.

fact that irradiation is not used in general practice with the same skill with which it is used in the larger clinics. This has also been emphasized by Figi in a recent study from the Mayo Clinic; he found the percentage of five year cures lower in his cases of secondary growth (previously treated by insufficient roentgen therapy, radium therapy and caustics), and a higher degree of malignancy and metastasis.

In table 4 is given a comparison of cases taken at random from the literature, to show the five year results of various forms of treatment. An attempt has been made as far as possible to choose similar cases,

although the groups are not absolutely identical. In the group taken from the department of surgical pathology at the Johns Hopkins Hospital, all the cases in which only local excision was done and the cases in which dissection of the cervical glands was done but no metastasis was found have been included. The same is true of the series which

TABLE 3.—*Treatment*

Type of Treatment*	Number of Cases	Number Cases Traced for 5 Years	Percentage of 5 Year Cures
Group 1. Excision of tumor only (no metastasis clinically)	176	149	80.9
Group 2. Excision of tumor and dissection of cervical glands (no metastasis).................	90	80	85.3
Group 3. Radical excision and dissection of cervical glands (metastasis present)...............	83	75	22.5
Operative mortality	3.7 per cent: 13 deaths in 349 surgical cases		
Hopeless (inoperable) carcinoma............................6.1 per cent: 24 of 390 cases			
Operation			349
Irradiation (primary treatment)...			4
Hopeless (palliative treatment)..			24
Insufficient data			13
Total number of cases..			390

* In 11 of the total 349 surgical cases postoperative irradiation therapy was given.

TABLE 4.—*Treatment of Carcinoma of the Lip*

Type of Treatment	Number of Cases Treated	Traced for 5 Years	Percentage of 5 Year Cures
Operation; all grades of cancer but no metastasis on first admission (Johns Hopkins Hospital).......................	266	228	82.4
Operation; primary treatment (no previous treatment) (Figi, Mayo Clinic)	...	217	80.3
Operation; primary treatment (no previous treatment) on first admission (MacMahon, Royal Prince Albert Hospital).......	351	228	90.3
Radium; primary treatment(no previous treatment) (MacMahon, Royal Prince Albert Hospital).................................	215	70	82.7
Radium; early cancer with no metastasis (Kelly-Kelly Radium Clinic)	...	67	81.7
Local destruction with or without irradiation: early cancer with no metastasis (Wile and Hand, Univ. of Michigan Clinic)....	...	49	53.8

received surgical treatment from the Royal Prince Albert Hospital in Sydney, Australia. No explanation is necessary for the other series which received irradiation and local destruction. The number of cases in which irradiation of the regional lymph nodes as well as of the primary lesion was given could not be definitely determined, but undoubtedly a considerable number of such cases existed.

The interesting points in the comparison are the good results obtained by operation and the uniformity of results obtained by MacMahon from

the Royal Prince Albert Hospital with the results of radium therapy reported by Kelly and the surgical results reported in this paper and by Figi from the Mayo Clinic. Whether the slightly better results obtained by operation is of any practical value as far as treatment is concerned, is questionable. MacMahon concluded that it is a sufficient difference. What statistics do not show but what seems important is that there is apt to be more uniformity of treatment by operation than by radiation. This seems logical because the knowledge, experience and skill necessary to calculate the proper dose of radiation is greater than that necessary for surgical excision with a sufficient margin of normal tissue. Another factor in favor of surgical treatment is that the whole specimen is obtained for microscopic study, so that a more accurate determination can be made as to prognosis and the need of further therapy. For a large superficial lesion involving both sides of the lip irradiation may be an easier procedure and may offer a better cosmetic result.

TABLE 5.—*Types of Carcinoma*

Type	Number
Carcinoma of the stomach	2
Carcinoma of skin, other than lip	2
Carcinoma of the tongue	1
Carcinoma of the esophagus	1
Carcinoma of the liver	1
Carcinoma of the penis	1
Carcinoma of the jaw	1
Total	9

No discussion has been given concerning treatment by dermatologic methods. The results reported by different observers [11] in the dermatologic field are too variable to permit conclusions regarding the value of cauterization. It is apparent, however, that with this method as with insufficient irradiation, recurrence is common and renders the prognosis with further treatment poor.

DEATH DUE TO OTHER CAUSES

During the five year period following treatment, there were 34 deaths due to intercurrent diseases in the 328 cases followed. The more common causes of death in their order of frequency were: cardiac disease, cerebral hemorrhage, disease of the kidneys, pneumonia, senility, injury, intestinal obstruction and jaundice.

11. Wile, U. J., and Hand, E. A.: Cancer of the Lip. J. A. M. A. **108**:374 (Jan. 30) 1937. Elliott, J. A.: Treatment of Epithelioma of the Lip by the Dermatologist, Arch. Dermat. & Syph. **27**:373 (March) 1933.

It is interesting to note the number of patients in whom carcinoma developed elsewhere in the body after treatment for carcinoma of the lip. In the series of 328 patients followed, 9 eventually showed other forms of cancer.

<div style="text-align:center">COMMENT</div>

When this study was undertaken, there were three questions which were of interest to me. They were: Is operation a satisfactory way to treat carcinoma of the lip? Is dissection of the cervical glands of real value as a prophylactic measure? Why is there so much apparent disagreement as to the proper way to treat carcinoma of the lip? The last question is satisfactorily answered by the fact that good results are now being obtained by both operation and irradiation for carcinoma in early stages. The second question is slightly more difficult. However, it would seem from the results in this series that in a selected group of cases in which the tumor showed a high grade of malignancy and invasion of the deeper structure of the lip, with or without clinical evidence of metastasis, dissection of the glands of the neck is a wise procedure. The answer to the first question is not difficult, for the results show that operation is a method of treating carcinoma of the lip which is as desirable as radium therapy or cauterization, and that the percentage of five year cures may perhaps be slightly higher.

<div style="text-align:center">SUMMARY</div>

A clinical and pathologic study of 390 cases of carcinoma of the lip is presented. The diagnosis has been made from the microscopic examination in all except 10 cases, all cases of hopeless carcinoma.

Statistics are given (table 2) as to the number of cases, type of carcinoma, age incidence, sex of the patient, average duration of the lesion, the presence or absence of metastasis or recurrence when the patient was first examined.

There were 344 cases of squamous cell carcinoma, 44 cases of basal cell carcinoma and 2 cases of adenocarcinoma. Only 2 per cent of the basal cell lesions occurred on the lower lip, and none of the adenocarcinomas.

There were 336 malignant lesions of the lower lip and 54 malignant lesions of the upper lip.

"Malignant wart" is a term used to indicate the papillary, squamous cell, low grade type of carcinoma.

Illustrations are shown (figs. 3, 4 and 5) to emphasize the fact that clinically a lesion cannot always be diagnosed as benign or malignant. Emphasis is put on the microscopic study in relation to prognosis and therapy.

Five year follow-ups were selected as the best index to results obtained in treatment. Follow-ups were obtained in 328 of the 390 cases. The percentage of five year cures for the entire series was 61.6.

The incidence of metastasis or recurrence on first examination was 36.4 per cent.

The results of treatment are reported for three groups; group 1, in which local excision alone was performed on 176 patients with no clinical evidence of metastasis, showed 80.9 per cent of five year cures. Group 2 included cases in which local excision plus dissection of the cervical glands was carried out, but no metastasis found microscopically. The percentage of five year cures in group 2 was 85.3. Group 3 consisted of 83 cases in which both local excision and cervical gland dissection were done, in which metastasis was found. The percentage of five year cures in group 3 was 22.5.

The operative mortality was 3.7 per cent in 349 cases; 8 deaths occurred in the more radical operations necessary in group 3, 4 deaths occurred in group 2. No operative deaths occurred in group 1.

In table 4 is given a comparison of five year results from the literature in patients treated by operation, irradiation and dermatologic methods. In this comparison, operation compares favorably with the other methods of treatment.

EPULIS

A SERIES OF CASES

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According to Römer,[1] the term epulis was first employed by Galen to designate a tumor on the gums. The term as used by him applied generally to any kind of abnormal gingival growth. In more recent times its use has been restricted, as a rule, to certain types of growth found in this region of the oral cavity, although some writers still use the word in its more general meaning.

This report records observations on a series of cases of epulis and does not pretend to discuss the proper use of the term or the kinds of tumor that might be included under it. As used here, "epulis" refers to a benign epithelium-covered connective tissue tumor found immediately around the teeth and having its origin in the pericementum or the periosteum of the marginal alveolar process.

The tumor will be described from the standpoint of (1) clinical manifestations, (2) clinical diagnosis, (3) roentgen findings, (4) treatment, (5) results of treatment, including early and later follow-up observations and (6) histologic appearance.

Virchow[2] pointed out that there is a certain convenience in speaking of epulis as sarcomatous, fibromatous or myxomatous. Lukomsky[3] stated that "according to its origin and character, epulis might be called an osteofibroma" and

In the development of epulides there are two forms which appear different at different times, (1) an earlier complex form with giant cells, and (2) a later pure fibromatous form.

1. Römer, O.: Die Epulis, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1938, vol. 4, pt. 2, p. 432.

2. Virchow, R.: Die krankhaften Geschwülste, in Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre: Zwanzig Vorlesungen über Pathologie, ed. 2, Berlin, A. Hirschwald, 1862, p. 292.

3. Lukomsky, J. H.: Die Epuliden, Deutsche Monatschr. f. Zahnh. 44:697, 1926.

Thoma [4] stated:

> When they are newly formed they are generally very vascular and red and bleed easily when injured. When of long standing they become more solid and firm, often losing their inflammatory character and changing to fibroma.

Garretson,[5] Blair and Ivy,[6] Rywkind,[7] Häupl [8] and others have differentiated between various types of proposed classifications of epulis based on the predominant type of tissue. In general (fig. 1) the groupings suggested by the various writers include (1) that in which the connective tissue predominates (fibromatous epulis), (2) that in which the vessels predominate (angiomatous epulis) and (3) that in which giant cells predominate (sarcomatous, or benign giant cell, epulis). Although the majority of epulides can be placed under these headings, some are
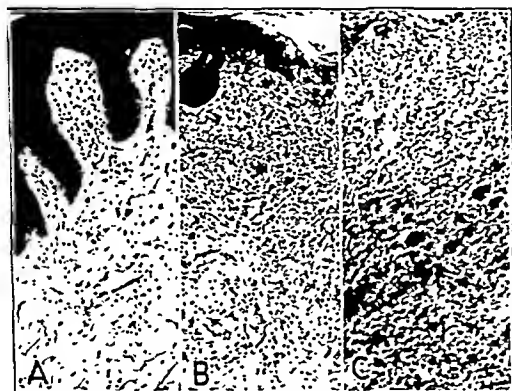
Fig. 1.—Photomicrographs (× 75) of histologic sections of (*A*) an epulis in which connective tissue predominates, (*B*) one in which vessels predominate and (*C*) one in which giant cells predominate.

encountered that do not belong in any of these categories. There are also many variations within each group.

4. Thoma, K. H.: Peripheral Tumors of the Oral Tissues, in Clinical Pathology of the Jaws with a Histologic and Roentgen Study of Practical Cases, Springfield, Ill., Charles C. Thomas, Publisher, 1934, p. 345.

5. Garretson, J. E.: The Tumors of the Mouth, in A System of Oral Surgery, ed. 2, Philadelphia, J. B. Lippincott Company, 1873, p. 819.

6. Blair, V. P., and Ivy, R. H.: Essentials of Oral Surgery, St. Louis, C. V. Mosby Company, 1925, p. 278.

7. Rywkind, A. W.: Die Epuliden und deren Beziehung zur Ostitis fibrosa, Virchows Arch. f. path. Anat. **263**:415, 1927.

8. Häupl, K.: Zur Kenntnis der sogenannten Riesenzellensarkome der Kiefer, Vrtljschr. f. Zahnh. **41**:449, 1925. Hesse, G.: Die Epulis, Leipzig, A. Pries, 1907.

Probably the only important characteristic that the giant cell epulis has in common with the regular giant cell sarcoma is the formation of giant cells. In the giant cell epulis, which is under consideration here, the giant cells may be many or few and may be scattered throughout the tumor or occur only in focal areas. In this series they occur only in the younger vascular epulides, found in the younger patients.

In the vascular type of epulis also there is considerable variation. In some tumors there seems to be a supply of blood vessels adequate only for normal nutrition. Others may be highly vascular, simulating true hemangioma. The blood vessels may be normal, small or large or may appear in the section as wide endothelium-lined blood spaces. They may be found in focal areas or generally distributed throughout the tumor.

Fibromatous epulis also shows great variation. The connective tissue may be of a uniform dense normal adult type, or young and either loosely woven or interspersed with strands of a more dense type. Some, such fibromas contain calcium salts in the form of (1) amorphous deposits of calcium, (2) round calcific masses scattered throughout the tumor, (3) spicules of bone and (4) regular laminated trabecular bone. The epulides containing osseous structures will receive particular attention in this report.

Ten of a group of 20 patients stated that the epulis began with a local mechanical injury. In most of these the injury was caused by a carious or broken-down tooth. The other patients were uncertain as to the beginning of the tumor.

The tumors were removed with the region under local anesthesia, 1 to 3 cc. of 2 per cent procaine hydrochloride with 1 to 3 minims (0.06 to 0.18 cc.) of 1:1,000 epinephrine being used. An incision was made around and 2 to 3 mm. beyond the margin of the tumor through to the underlying hard structures. The entire mass was elevated and removed, and the region of the attachment was thoroughly curetted. A blood clot was then allowed to form, and the patient was dismissed. As a rule it was not necessary to employ sutures. The patients were seen from ten days to two weeks after the operation, satisfactory healing taking place during the interval. Regular instruction in oral hygiene was given, but there was no further postoperative treatment.

Teeth which seemed to be undergoing displacement from their sockets by the growth of the tumor mass were removed, with involved portions of their immediate supporting structures (fig. 2). This operation was performed in 4 of the 20 cases.

In 1 instance the normal eruption of the upper left permanent first incisor had been impeded by the growth of the tumor around the

crown of this tooth and the resorbing root of its deciduous predecessor. Eruption of the permanent incisor into normal occlusion followed the removal of the tumor (fig. 3). When teeth had been merely tilted

Fig. 2.—Photograph, natural size, of an epulis in the left anterior portion of the mandible. The tumor has displaced several teeth by its growth.
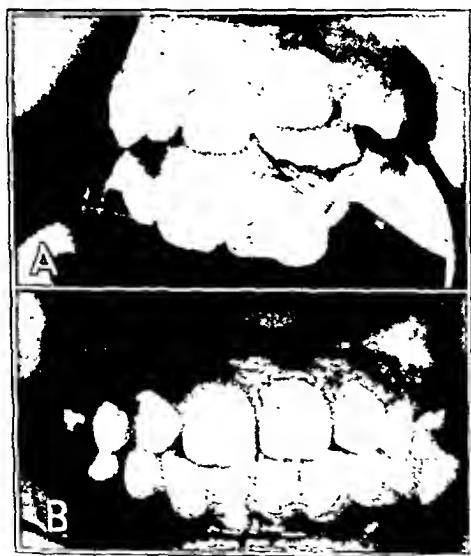
Fig. 3—Photographs, natural size, of (*A*) an epulis in the left anterior portion of the maxilla which apparently prevented the proper eruption of the permanent first incisor; (*B*) the same region one year after the removal of this tumor, showing the teeth in normal occlusion.

out of alinement by the growth, a return to their normal positions in the dental arch followed the removal of the tumor (fig. 4).

Nine of the 20 patients have been followed for less than one year, 1 for between one and two years, 5 for two to three years, 1 for between
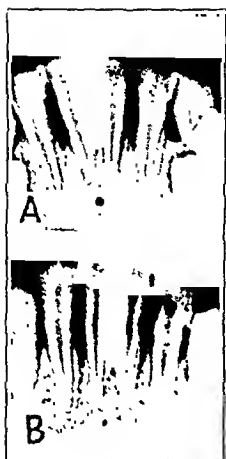
Figure 4

Figure 5

Fig. 4.—Roentgenograms of the mandibular permanent incisors, showing (*A*) the positions of these teeth before the removal of a small epulis situated between the crowns of the first two incisors; (*B*) the spontaneously corrected positions of these teeth, observed one year after removal of the tumor.

Fig. 5.—Roentgenograms showing (*A*) the position of the maxillary left second bicuspid and the bony projection into the central portion of an epulis situated in this region; (*B*), the condition one year after excision of the epulis, the second bicuspid and the bony growth.

Fig. 6.—Photomicrograph (× 75) of an epulis which had its attachment between the mandibular right second incisor and cuspid. Note the various stages of osseous development, ranging from the earliest signs of calcification to mature bone.

three and four years and 4 for four to five years. No tumor so far has shown any evidence of recurrence.

The histologic preparations showed that 3 tumors in the series of 20 contained giant cells; 7 contained regular laminated trabecular bone demonstrable as a part of the tumor mass, and all showed varying degrees of chronic inflammatory reaction with increased vascularity. In 1 instance the bone occurred as an outgrowth of the alveolar process. providing a firm support for the tumor (fig. 5). In another, various stages of osseous development were observed, ranging from the earliest signs of calcification to the presence of mature bone (fig. 6).

It is of particular interest that osseous structures were present in 6 tumors which, according to the history and physical examination, had been subjected to direct masticatory stress for a year or more. Furthermore, these structures occurred only in patients in the third decade of life or beyond. In 1 instance regular bone was found in one of the older tumors that had not been in occlusion.

SUMMARY

The various types of epulis, classified according to their characteristic histologic structure, may represent different stages of development of the same growth.

In this series only the younger epulides, found in the younger patients. contained giant cells. The older epulides, found only in patients in the third decade of life or beyond. contained regular laminated trabecular bone.

This type of osseous structure in all but 1 instance followed masticatory stress directly to the tumor mass.

The majority of the patients stated that the epulis began with a local mechanical injury to the place of origin.

Indications for the extraction of teeth displaced by the tumor may be determined partly by the direction of displacement.

POSSIBILITY OF DIFFERENTIAL SECTION OF THE SPINOTHALAMIC TRACT

A CLINICAL AND HISTOLOGIC STUDY

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By 1905 Spiller[1] had conceived of an isolated tract in the spinal cord mediating pain. In 1911 Martin,[2] at Spiller's suggestion, did the first chordotomy to relieve pain. This operation, which has come to be known as the Spiller-Frazier operation, or, more commonly, as chordotomy, has been done many times since its introduction, and numerous reports have testified to its efficacy and value.

In doing 41 chordotomies during the past three years, one of us (O. H.) saw reason to question the accepted location of the spinothalamic tract as well as the accepted disposition of its fibers. We are reporting 6 cases in which the operation was done with the patient under local anesthesia only. Sections were made in the cord according to various patterns, and cutaneous sensibility was tested at the operating table.

GENERAL FACTORS RELATED TO CHORDOTOMY

Segment of Election.—The most popular locations for section have been the regions of the first, second and third thoracic segments and the fifth, sixth and seventh thoracic segments, or, more specifically, that part of the cord beneath the second, the third or the sixth laminal arch. All of our sections have been made beneath the second or the third arch, but a lower site has the advantage of not being between the shoulder blades and is satisfactory if the patient's pain is not located higher than the groin.

1. Spiller, W. G.: The Occasional Clinical Resemblance Between Caries of the Vertebrae and Lumbothoracic Syringomyelia, and the Location Within the Spinal Cord of the Fibres for the Sensations of Pain and Temperature, Univ. Pennsylvania M. Bull. **18**:147-154, 1905.

2. Spiller, W. G., and Martin, E.: The Treatment of Persistent Pain of Organic Origin in the Lower Part of the Body by Division of the Anterolateral Column of the Spinal Cord, J. A. M. A. **58**:1489-1490 (May 18) 1912.

Foerster [3] has made sections at every cervical segment to and including the second and has obtained anesthesia in correspondingly high distributions. He has advised against bilateral cervical sections, however, at least at the same time, because of interference with respiration.

In order to eliminate pain in the upper extremity it is necessary to make a high cervical section and this has been done successfully. Peet, Kahn and Allen [4] reported a case of bilateral cervical chordotomy, one section being made at the third cervical and the other at the eighth cervical segment. The higher section eliminated pain in the contralateral arm.

Frazier and Spiller [5] reported a case in which section at the first thoracic segment resulted in involvement of the pupillary center.

Fay and Gotten [6] by using spinal anesthesia have given evidence to show that section made as low as the fifth thoracic segment may not abolish all pain in the lower extremity even though cutaneous pain may be lost. They suggested that some types of pain probably reach the cord at a higher level by way of the vessels and the sympathetic nerves. They found that a section above the third thoracic segment does abolish all types of pain. These findings may be of value in determining the site of election.

Motor Effects of Anterior Chordotomy.—Permanent motor impairment other than degrees of paralysis from injury to the pyramidal tracts has been uniformly absent. This is true of the cases in the literature as well as of our own cases. Despite the supposed function of the ventral spinocerebellar tract and the descending extrapyramidal tracts, no evidence of ataxia or incoordination has been elicited. One of our most striking cases was that of a patient with tabetic crises, in whom practically the entire anterior half of the cord was sectioned. That is, deep bilateral sections were made from the dentate ligaments to the anterior median fissure. There was flaccid paralysis for five days, and then progressive recovery to normal tone and motor function of the lower extremities within a month. No evidence of ataxia or incoordination

3. (*a*) Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932. (*b*) Foerster, O.: Ueber die Vorderseitenstrangdurchschneidung, Arch. f. Psychiat. **81**:707-717, 1927.

4. Peet, M. M.; Kahn, E. A., and Allen, S. S.: Bilateral Cervical Chordotomy, for Relief of Pain in Chronic Infectious Arthritis, J. A. M. A. **100**:448-489 (Feb. 18) 1933.

5. Frazier, C. H., and Spiller, W. G.: Section of the Anterolateral Columns of the Spinal Cord (Chordotomy), Arch. Neurol. & Psychiat. **9**:1-21 (Jan.) 1923.

6. Fay, T., and Gotten, N.: Controlled Spinal Anesthesia: Value in Establishing Appropriate Levels for Chordotomy, Arch. Neurol. & Psychiat. **30**:1276-1281 (Dec.) 1933.

was observed. The patient was a carpenter and worked on scaffolding with a sure footing. It appears that in man the descending extrapyramidal tracts are not indispensable to normal tone and motor function.

Cadwalader and Sweet [7] found that ataxia and incoordination were marked in dogs after section of the anterolateral column and attributed the disturbances of function to section of the ventral spinocerebellar tracts and probably the rubrospinal and vestibulospinal tracts.

Sensory Effects of Anterior Chordotomy.—We believe that complete section of the spinothalamic tracts on one side at or above the third thoracic segment will abolish all pain and sense of temperature on the contralateral side from two or three segments below the section downward. This loss is permanent, and there has been no evidence of a bilateral representation of pain or temperature. In cases in which there appears to have been some return of "pain spots," the section has been incomplete.

If the section has not been made deep enough, the loss of pain sensibility will be greater during the first few postoperative days than subsequently.

If the section has been incomplete in an anterior-posterior direction the level of the loss of pain may retract toward the area of permanent loss a week or so after the operation. This appears to be true in regard to upper and lower levels in our cases of differential section (see case 6). That is, if some of the posterior fibers of the column are spared, the level of sensory impairment will subsequently retract upward; if some of the anterior fibers of the column are spared, the level will retract somewhat downward.

There has been equal impairment in discrimination of both pain and temperature in all of our cases. One has the impression that at the upper levels of sensory impairment one of these modalities may shade off more rapidly than the other, but interpretations are difficult. For example, one of our patients seemed to sense cold but not heat at the upper level of transition. The fact that discrimination of pain and discrimination of temperature have been segregated in cases of tumor of the cord is more probably due to differences in vulnerability than to differences in anatomic location of tracts mediating pain and temperature.

Frazier and Spiller [5] expressed the belief that fibers conducting pain and temperature do not ascend uncrossed and also that pain, heat

7. Cadwalader, W. B., and Sweet, J. E.: Experimental Work on the Function of the Anterolateral Column of the Spinal Cord, J. A. M. A. *58:1490-1493* (May 18) 1912.

and cold are eliminated together, so that the fibers subserving these modalities must be mixed together.

So far as we know, Stookey [8] is the only one who has abolished the sense of pain without destroying the sense of temperature. He inserts the knife at the dentate ligament and brings it out just lateral to the anterior horn. He feels that the anterior spinothalamic tract probably conducts the sense of temperature, although his operation is the same as that performed by others.

It has been felt by many (including Head) that the tractus spino-thalamicus ventralis mediates touch. Frazier and Spiller [9] could give no testimony to this, as their sections had not extended beyond the anterior horn.

One of us (O. H.) has made numerous deep sections extending to the anterior median fissure, and in no case were we able to elicit by the routine methods any loss in perception of light touch or of deep pressure, in two point discrimination or in the sense of position.

In none of our cases have we failed to eliminate pain. The series includes 3 cases of gastric crises, 2 of which are reported here (cases 2 and 5). The upper level of loss of pain reached the nipple line bilaterally in all 3 cases.

More striking than the prompt and permanent relief of demoralizing pain was the abolition, also permanent, of the vomiting or motor element of the crises.[10]

Oldberg [11] stated:

There are certain things one must not expect this operation to do. One of them is to relieve the vomiting which is so often associated with gastric crises of tabes dorsalis. This vomiting is vagal in character and so, of course, would not be affected by a spinal cord operation.

Although this would naturally be one's first impression, the facts are fortunately more favorable.

Kahn and Barney [12] reported an interesting case in which bilateral chordotomy was done at the fifth thoracic segment in a patient suffering from gastric crises. The level of loss of pain was at the umbilicus, and the crises were not relieved. The splanchnic nerves were sectioned, and

8. Stookey, B.: Human Chordotomy to Abolish Pain Sense Without Destroying Temperature Sense. J. Nerv. & Ment. Dis. **69**:552-557 (May) 1929.

9. Spiller, W. G., in discussion on Frazier, C. H.: Section of the Antero-lateral Columns of the Spinal Cord for the Relief of Pain: Report of Six Cases, Arch. Neurol. & Psychiat. **4**:575-576 (Nov.) 1920.

10. Case 5 is a possible exception.

11. Oldberg, E.: Chordotomy for Relief of Pain, S. Clin. North America **12**: 1315-1322 (Oct.) 1932.

12. Kahn, E. A., and Barney, B. F.: Anterolateral Chordotomy for Intractable Pain of Tabes Dorsalis, Arch. Neurol. & Psychiat. **38**:467-472 (Sept.) 1937.

later the rami communicantes of the eleventh and the twelfth thoracic nerves. The pain being still unrelieved, bilateral chordotomy was done at the seventh cervical segment, and this was followed by complete relief.

Our conclusion is that gastric crises (both pain and motor elements) can be eliminated, but a bilateral section must be made at or above the third thoracic segment, so as to include the chest in the region of analgesia.

Other Factors.—Retention of urine necessitating catheterization for ten to fourteen days has occurred in our cases after complete bilateral section beginning at the dentate ligament. Retention has not occurred after unilateral section. This has been the experience of Sicard and Robineau.[13] In case 6, in which minimal differential bilateral section was done, postoperative retention of urine lasted only two days, even though the patient had shown impairment of vesical tone preoperatively. We feel that this unpleasant sequel of bilateral section will be greatly obviated if complete section of the pain tract is performed with minimal destruction of the cord, as is subsequently suggested.

Patients cannot distinguish wetness in involved zones. They distinguish hair pulling, but without pain. The sensation of tickling was lost on the soles in 2 patients and was retained in others. The subjective sensation in the lower extremities has invariably been one of warmth and comfort.

Bilateral section destroys in the male the ability to have sexual intercourse and orgasms, though it does not always destroy sexual desire. Erection was impossible in one patient. One woman reported that the voluptuous sensation of intercourse was lost. No patient so far has regretted the operation because of this sequela.

One of the most intriguing facts related to chordotomy is that the patient feels no pain when the spinothalamic tract is cut, nor has a patient ever complained of referred pain in the distribution of the severed tract comparable to that occurring after section of a nerve root. Feeling that impulses of pain must be combined with those of touch in order to be properly interpreted, one of us (O. H.) had his assistant stroke the posterior columns while the "pain tract" was being cut. Although the patient felt a constricting pressure about the groins, he denied that there was pain. This is another evidence that artificially provoked impulses in neurons of the second order have an unexpected and entirely different physiologic result from such impulses in neurons of the first order.

Girdle pain commonly follows chordotomy and is proportional to the degree to which the posterior roots have been manipulated. It is some-

13. Sicard and Robineau: Cordotomie latérale antérieure pour algies incurables, Rev. neurol. **1:**21-28 (Jan.) 1925.

times troublesome for a long period if filaments of a posterior root were unwittingly crushed when the dentate ligament was grasped. Great care should be exercised in dissecting the dentate ligament free from both posterior and anterior root filaments. Should a posterior root be injured it is preferable to sever it entirely.

In a case of medulloblastoma with metastases to the cord the anterior spinal artery was accidentally cut. Complete paralysis ensued, which we feel was attributable to ischemia.

TOPOGRAPHIC ANATOMY OF THE CORD

It appears that insufficient attention has been given to the precise location of the dentate ligaments and the line of entry of the anterior roots as the operator sees them.

It has usually been implied that the coronal plane of the dentate ligaments equally divides the cord. In a study of several cords we observed that this plane more nearly passes through the junction of the posterior third of the cord with the anterior two thirds.

The line of entry of the anterior roots does not correspond with the position of the anterior horns as it is often represented to do but is situated lateral to the horns. The line formed as the anterior roots enter the cord is definite and is slightly more than half the distance from the dentate ligament to the anterior median fissure.

We have prepared the diagrams which accompany the case reports to represent a close reproduction of the topography of the cord. The statements made here and the diagrams, of course, have reference to the thoracic portion of the cord at the level of the third dorsal vertebra.

TECHNIC

In the cases to follow, all sections of the cord were made beneath the second or the third dorsal laminal arch. When bilateral sections were made, they were separated by ½ to 1 inch (1.2 to 2.5 cm.). Posterior roots were sectioned only in cases in which it is specifically stated that they were. All operations were done with the region under local anesthesia (2 per cent procaine hydrochloride in the skin and 0.5 per cent procaine hydrochloride in the muscles to the transverse processes). The initial infiltration was sufficient. None of the patients complained of pain when bone was removed or during any part of the operation except when direct manipulation or pinching of a posterior root occurred. They were cooperative during the sensory tests. Some of these were made by one of us (C. Van E.) and some by Dr. J. W. Dulin.

The sections were made with a narrow-bladed cataract knife.

REPORT OF CASES

Case 1.—D. C., a white man aged 38, entered the hospital on March 5, 1938, complaining of severe and constant pain in the left hip and leg. In August 1937 a disarticulation of the right humerus had been done for osteochondrosarcoma. On admission to the hospital on March 5 there was roentgen evidence of metastases in the chest and in the fourth lumbar vertebra.

Chordotomy was done as indicated in figure 1. The patient was comfortable and free from pain at the time he left the hospital, four weeks later.
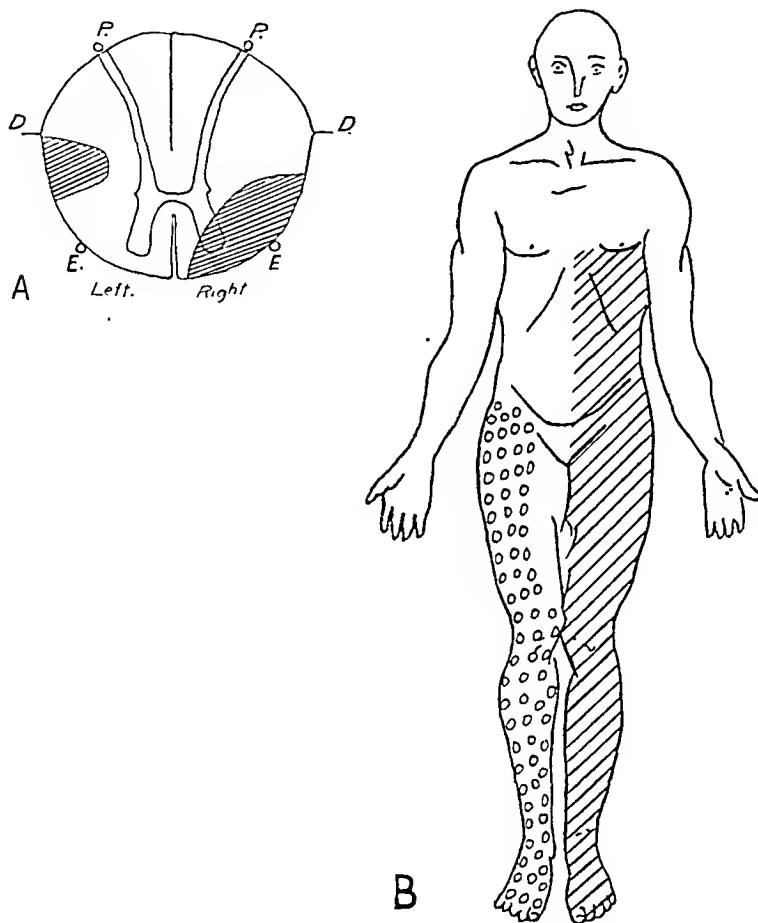
Fig. 1 (case 1).—*A*, diagram indicating the manner in which the cord was sectioned. *P*, line of entry of the posterior roots; *D*, dentate ligament; *E*, line of entry of the anterior roots. *B*, drawing to show the results of the sections. The cross hatching indicates complete loss of pain and of temperature sense. The circles indicate partial loss in these modalities. There appeared to be areas roughly 0.5 cm. in diameter which would be normally sensitive to pain, whereas in an adjacent similar area pain was lost.

Case 2.—L. K., a white man aged 56, entered the hospital in March 1938 because of gastric crises. He had contracted syphilis in 1913, and for three and one-half years prior to his admission to the hospital he had gastric crises (abdominal pain and vomiting) progressing in severity.

Antisyphilitic therapy produced negativity of the Wassermann reaction, and there was relatively little evidence of damage to the posterior columns of the spinal cord. The gastric crises, occurring several times a week, were severe, and for three months he had had continuous pain girdling the chest.

Chordotomy was done as indicated in figure 2. The patient voided urine voluntarily from the first day after the operation. He has remained free from crises (both pain and vomiting) to the present writing (six months).
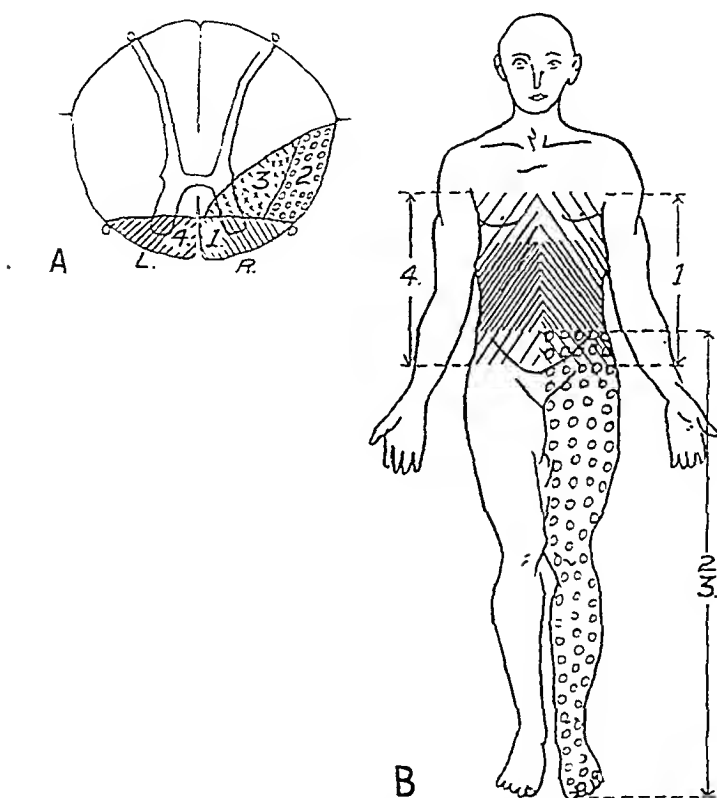
Fig. 2 (case 2).—A, diagram indicating the manner in which the sections were made. The numbers indicate the order in which the sections were made. B, drawing to show the results of the sections. The close hatching indicates complete loss of pain and of temperature sense. The wide hatching indicates about 50 per cent loss in these modalities. The circles indicate complete loss in both modalities, but this was not fully obtained until section 3 was made.

CASE 3.—J. H., a white man aged 67, entered the hospital on July 11, 1938, complaining of severe postherpetic neuralgia in the distribution of the eighth, ninth and tenth thoracic nerves on the left. He had had herpes zoster in January.

Unilateral chordotomy was done as indicated in figure 3. Complete relief was obtained. For technical reasons, the third dorsal posterior root was sectioned on

each side. This produced an indefinite sensory loss on the right side of the chest, which is not indicated in the diagram.

There was no difficulty in voiding urine at any time after the operation.
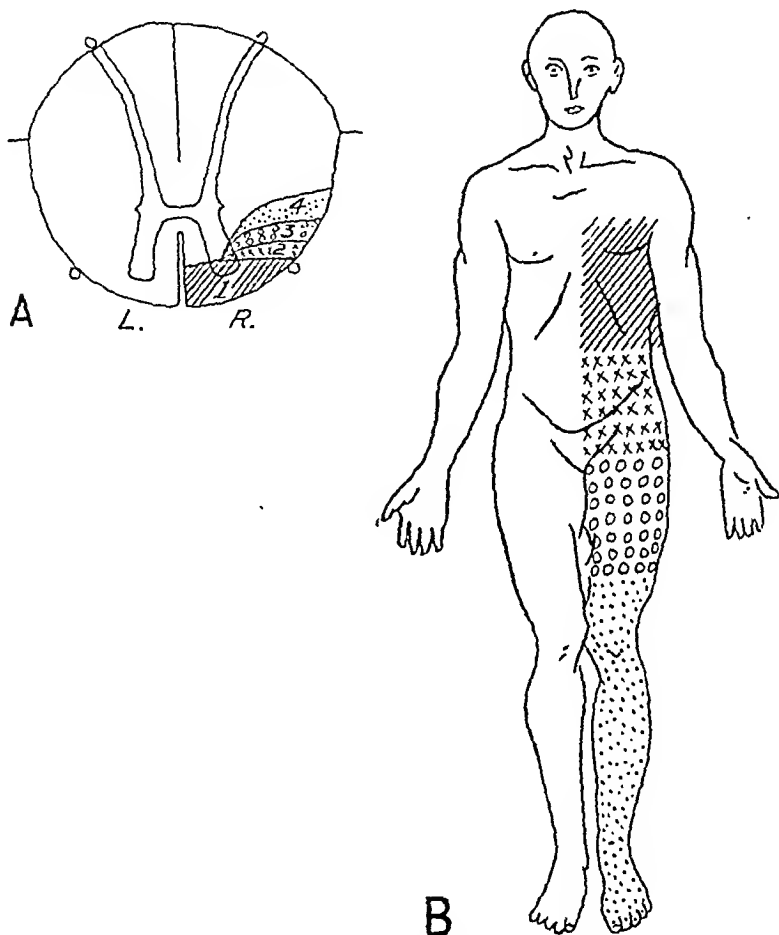
Fig. 3 (case 3).—*A,* diagram indicating the manner in which sections were made. *B,* drawing to indicate that a final complete loss of pain and of temperature sense reached a level at about the nipple line. Note that the level in this case was caused to progress downward, the reverse of that in the following cases. After section 1 the patient stated that he no longer felt the old pain, and the skin, which had been scarred by herpes, could now be rubbed without discomfort. This section, which caused a loss of pain and of temperature sense limited to the left side of the chest, would probably have been sufficient.

CASE 4.—H. S., a white man aged 24, entered the hospital April 14, 1938, complaining of relentless pain in the back and thighs. In May 1936 an abdomino-perineal resection of the rectum had been done because of carcinoma. Metastases were evident in the inguinal nodes and the bladder when he entered the hospital in 1938.

Morphine afforded little relief, and chordotomy was performed. The sections were made as indicated in figure 4.

Inasmuch as control of the bladder had been lost for some time, return of vesical function was not expected.

The patient was comfortable and entirely free from pain until his death on the sixteenth postoperative day.

The results of studies on the cord are shown in figure 5.
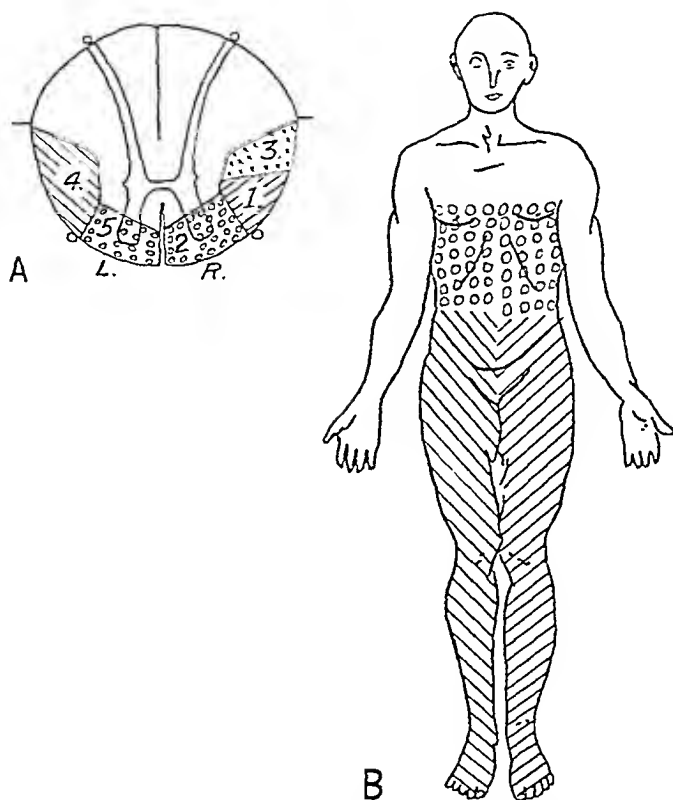
Fig. 4 (case 4).—*A*, diagram indicating the manner in which the sections were made. The numbers indicate their order. *B*, circles and hatching indicating complete loss of pain and of temperature sense. Note that sections 1 and 4 produce about the same upper level; section 3 had no additional effect, and sections 2 and 5 raised the level to the nipple line.

CASE 5.—C. K., a white man aged 27, entered the hospital in April 1938, complaining that he had suffered from attacks of abdominal pain and vomiting for three years. The attacks of vomiting began first, the painful element being superimposed later. At least one attack occurred each week and was typical of a gastric crisis except that the vomiting seemed more severe than the pain. Extensive antisyphilitic therapy had been given, but the Wassermann reaction was positive. There was only mild damage to the posterior columns, as demonstrated by clinical tests.

Chordotomy was carried out as indicated in figure 6.

The patient began to void urine normally by the fifteenth postoperative day.

To the present time, four months after the operation, he has had no pain and has vomited only twice.

CASE 6.—P. Z., a man aged 64, entered the hospital on April 25, 1938, with a complaint of pain in the abdomen and in the back. A supraclavicular node con-
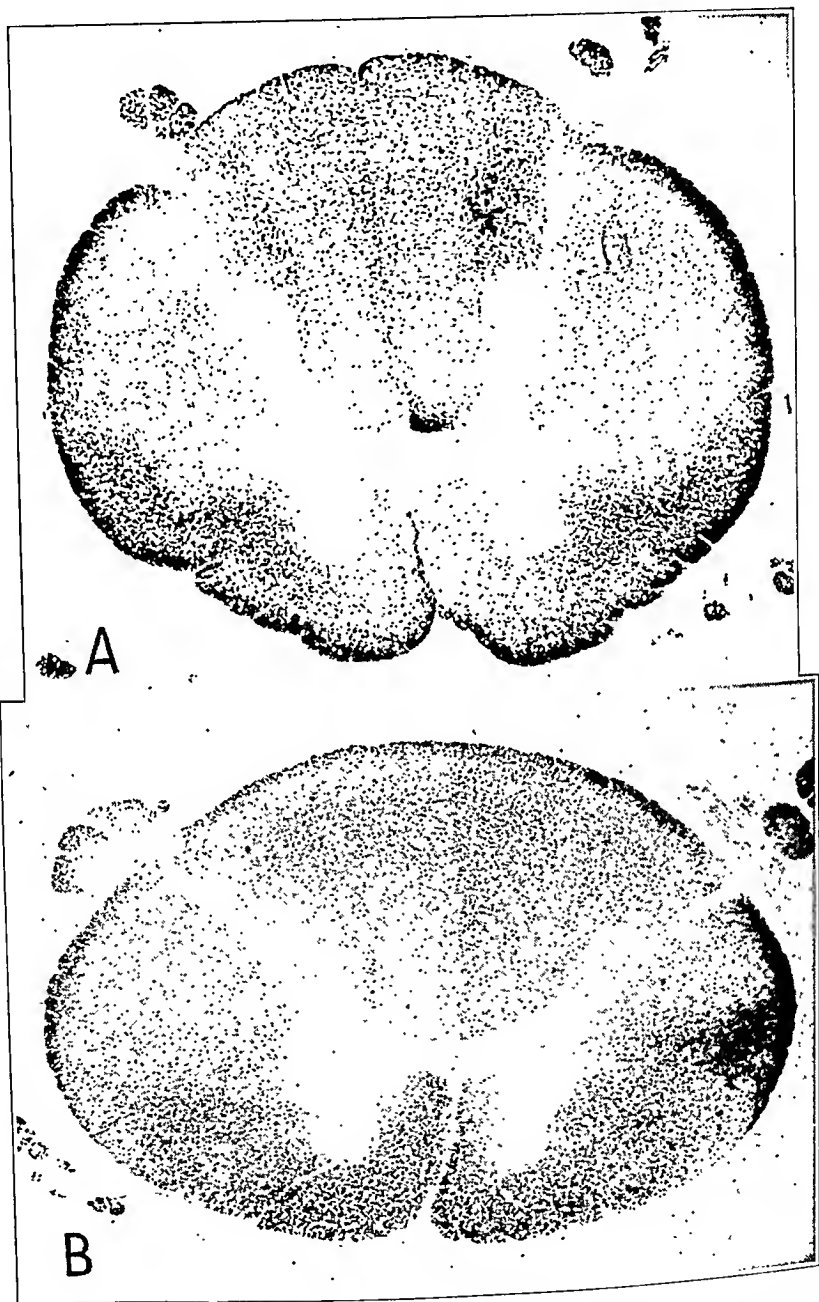
Fig. 5 (case 4).—*A*, Marchi preparation showing degeneration of the ascending fibers at the first thoracic level. (See figure 10 *E*, which is a diagrammatic tracing of this photograph.) *B*, Marchi preparation showing degeneration of the descending fibers at about the level of the fifth thoracic segment.

tained an adenocarcinoma, and a provisional diagnosis of carcinoma of the pancreas with diffuse abdominal metastases was made. Pain in the back, epigastrium and abdomen became so acute that the patient eagerly consented to chordotomy.

When the sections were made as indicated in the diagram (fig. 7) the patient stated that his pain had disappeared. Sensory tests substantiated his statement, and no further sections were made. The operation appeared to be no ordeal, and the patient was most grateful for complete relief from pain during his last days.
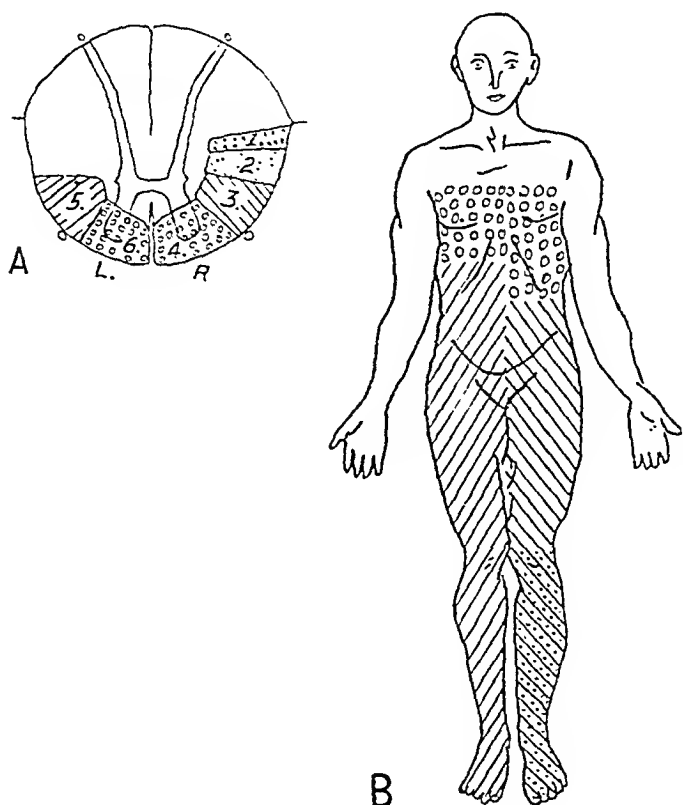
Fig. 6 (case 5).—*A*, diagram indicating the manner in which the sections were made. *B*, drawing to indicate the final complete loss of pain and of temperature sense, reaching a level at the nipple line. Section 1 made no detectable changes. Section 2 resulted in a spotty (50 per cent) loss of pain from the left knee down.

Vomiting, which had been persistent for two weeks, continued as before. Although he had had moderate difficulty in voiding urine before the chordotomy, this function was restored on the third postoperative day. He clearly perceived fulness of the bladder and desire to void.

He died on the twelfth postoperative day, and the results of a study of the cord are shown in figures 8 and 9.
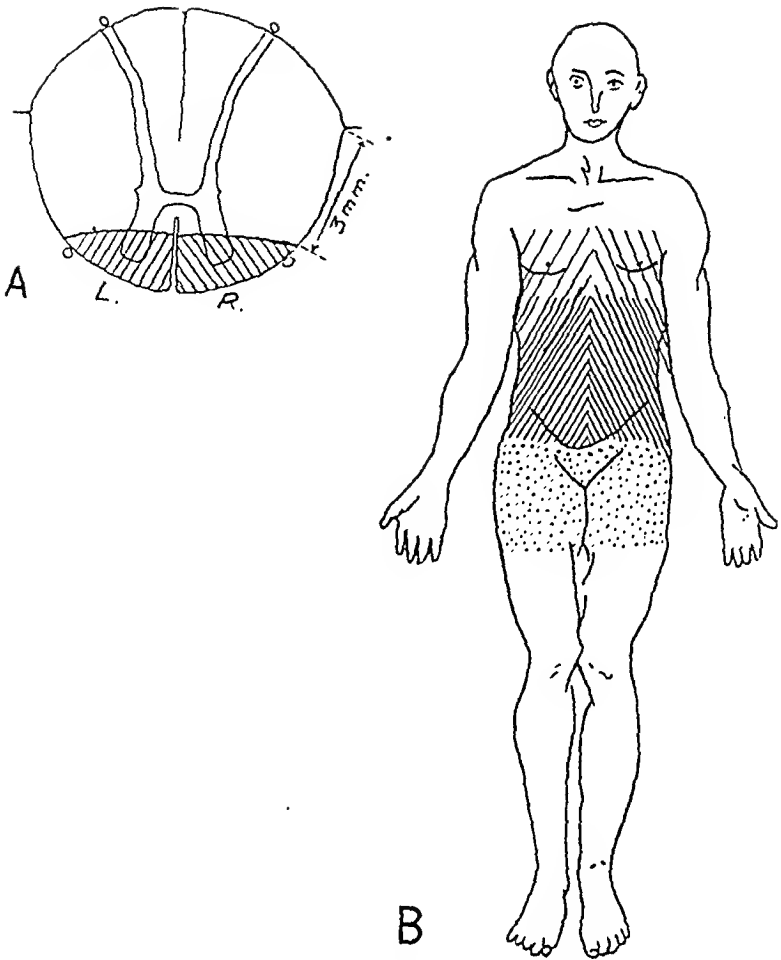
Fig. 7 (case 6).—*A,* diagram indicating the manner in which the cord was sectioned. *B,* drawing to show the results of the sections. The close hatching indicates loss of pain and of temperature sense, shading off above at the area of wide hatching and below at the stippled region. The loss of pain was complete in the stippled region on the day of operation, but this level retracted by the third postoperative day.
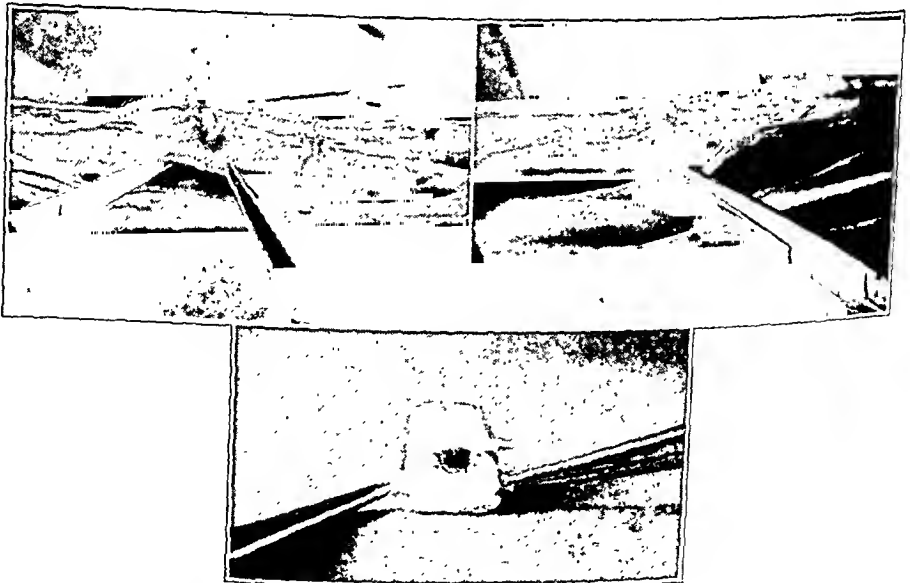
Fig. 8 (case 6).—Photographs showing the sections at different levels and a cross section of the cord through the lower section. In making each section the knife was inadvertently carried across the anterior median fissure but fortunately without cutting the anterior spinal artery. Hemostats are shown grasping the dentate ligaments in each case, and the distance from the ligament to the section can be clearly seen.

COMMENT

Optimum Location and Extent of Section.—So far as we know, all surgeons have begun their sections just anterior and close to the attach-
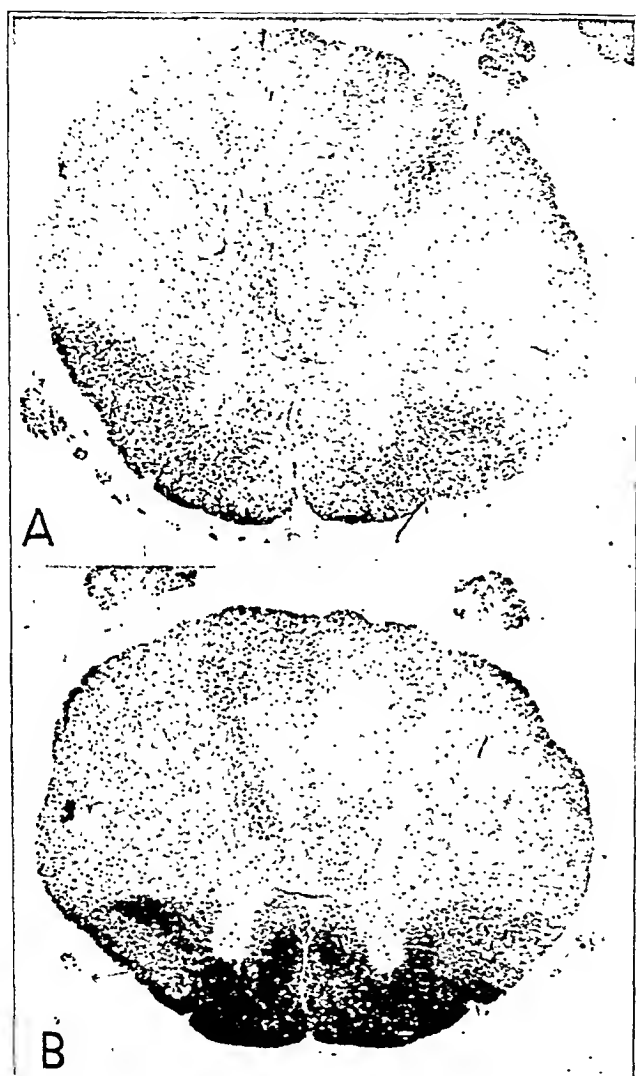
Fig. 9 (case 6).—*A*, Marchi preparation showing degeneration of the ascending fibers at the level of the first thoracic segment. Some of the posterior fibers have been spared. Compare with figure 5 *A*. *B*, Marchi preparation showing degeneration of the descending fibers between the levels of the fourth and fifth thoracic segments.

ment of the dentate ligament. According to the earlier literature the section was carried to or not quite to the anterior roots. However,

as more cases were studied, certain authors recognized that better results were obtained if more of the cord was included anteriorly. Peet[14] gained the impression that levels of sensory loss were higher if the incision was carried through, and not merely to, the anterior root.

Kahn and Barney[12] felt that the section should be carried 2 mm. beyond the anterior root.

Frazier[15] in 1 of a series of 6 bilateral chordotomies failed to obtain a sensory loss on one side.

Horrax' cases[16] indicate that his sections were not carried far enough anteriorly when the chordotomy was at a high thoracic level and high levels of sensory loss were desired. His routine section appeared sufficient when carried out at or below the level of the eighth thoracic segment. His cases also suggest that partial losses in an involved zone are due to failure to make the sections deep enough.

Sections carried to the anterior root may prove to be complete when done at low thoracic levels. As to this we are not prepared to make a statement at present, although our Marchi preparations indicate that the spinothalamic tract extends farther forward than the anterior root —at least as low as the fifth thoracic segment. Foerster's[3] preparations indicate that the fasciculus migrates posteriorly as the upper cervical segments are transgressed.

Leighton[17] made his incisions 2.5 mm. deep and 3 mm. wide, beginning at the dentate ligament and ending just behind the anterior roots. The sections were made under the fifth, sixth and seventh thoracic laminal arches, and the levels of sensory loss, when mentioned, were said to be about six segments lower. He endorsed the advice of Spiller that the section might with advantage be carried forward to include the anterior root.

The first chordotomy reported[2] is also interesting in this respect. Martin, who did the operation, stated:

The problem presented by Dr. Spiller was the making of a transverse cut into the spinal cord, roughly 2 mm. in length, of a similar depth, and with its posterior end 3 mm. anterior to the entrance of the posterior root, this cut to be bilateral.

14. Peet, M. M.: The Control of Intractable Pain in Lumbar Region, Pelvis and Lower Extremities by Section of the Anterolateral Columns of the Spinal Cord (Chordotomy), Arch. Surg. **13**:153-204 (Aug.) 1926.

15. Frazier, C. H.: Section of the Anterolateral Columns of the Spinal Cord for the Relief of Pain: Report of Six Cases, Arch. Neurol. & Psychiat. **4**:137-148 (Aug.) 1920.

16. Horrax, G.: Experiences with Chordotomy, Arch. Surg. **18**:1140-1164 (April) 1929.

17. Leighton, W. E.: Section of the Anterolateral Tract of the Cord for the Relief of Intractable Pain Due to Spinal Cord Lesions, Surg., Gynec. & Obst. **33**:246-249 (Sept.) 1921.
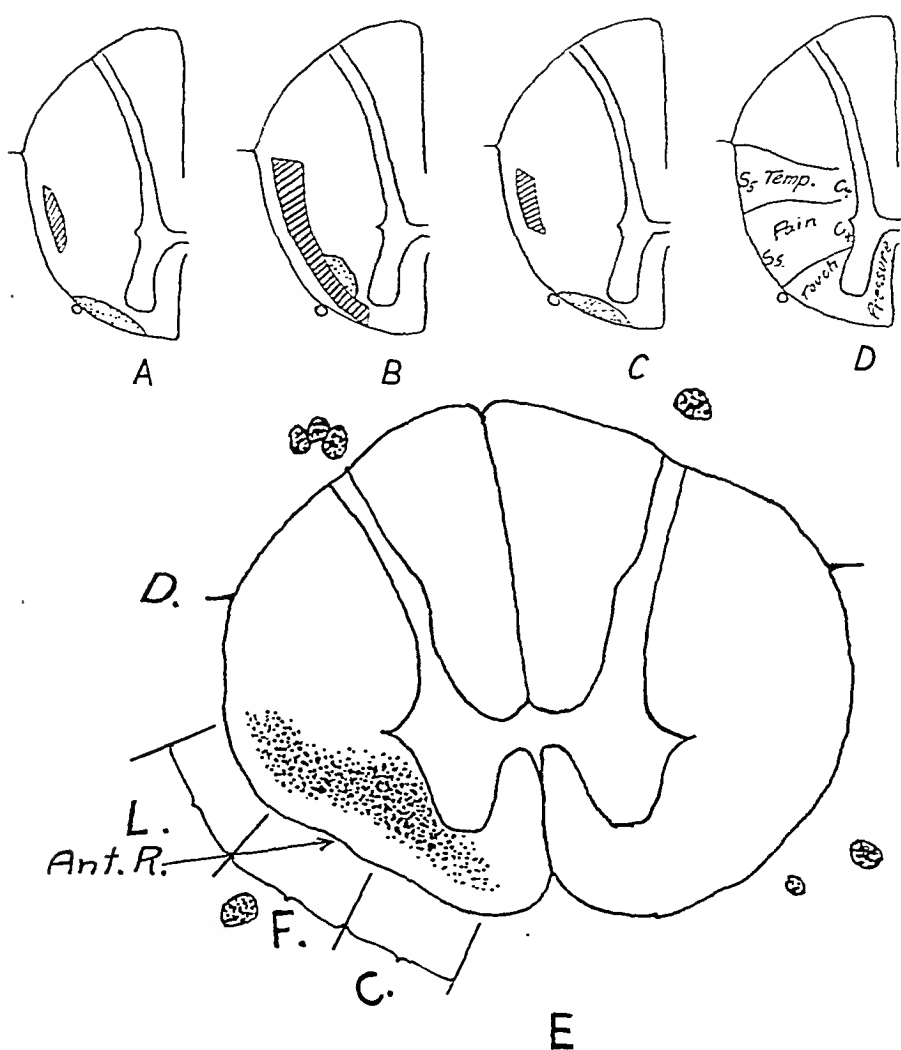
Fig. 10.—Diagrammatic representations of the spinothalamic tracts as given by several authors. *A*, drawing taken from Gray (Gray, H.: Anatomy of the Human Body, ed. 20, edited by W. H. Lewis, Philadelphia, Lea & Febiger, 1918, p. 759). *B*, drawing taken from Tilney and Riley (Tilney, F., and Riley, H. A.: The Form and Functions of the Central Nervous System, New York, Paul B. Hoeber, 1923, p. 196). *C*, drawing taken from Ranson (Ranson, S. W.: The Anatomy of the Nervous System, Philadelphia, W. B. Saunders Company, 1920, p. 110). *D*, drawing taken from Foerster.[5] *E*, our own concept of the tract, made from a tracing of figure 4 *A*.

L, fibers probably representing the lower extremity; *F*, fibers representing the groin and abdomen; *C*, fibers representing the chest; *D*, dentate ligament; *Ant. R*, line of anterior roots.

Spiller stated that objective sensation was lost in the anterior surfaces of the thighs but that pain and pinprick sensations were keen over the lower portion of the abdomen.

From a study of our cases we feel that the spinothalamic tract in the high thoracic region extends from a coronal plane about two-fifths the distance from the dentate ligament to the anterior roots to a sagittal plane about three-fifths the distance from the anterior root to the anterior median fissure (fig. 10 *E*). The tract broadens out in the region lateral to the anterior horn so that it hugs close to the latter structure and well fills the area between the anterior and the lateral horn. The minimal section, to include all the fibers of the spinothalamic tract should begin about 2 mm. anterior to the dentate ligament and emerge 2 to 3 mm. mesial to the anterior roots. The section should extend deep enough to skirt the lateral and anterior horns, 3 mm. of actual depth being sufficient. Patients in whom sections have been made in this manner have given clinical evidence of complete section of the tracts mediating pain and temperature. The 2 mm. region adjacent to the dentate ligament we feel contains no fibers conducting sensations of pain or temperature.

Disposition of Fibers Conducting Pain.—Foerster[3] has proposed that the fibers are arranged in a laminated fashion—those from the lowermost segments of the body occupying a place at the periphery of the tract and those of the higher segments disposing themselves toward the center of the cord (fig. 10 *D*). This concept appears to have been generally accepted.

Our studies indicate that fibers representing the lower segments are situated posteriorly in the tract and fibers representing successive segments upward dispose themselves more and more anteriorly (fig. 10 *E*).

Hence it has been possible to eliminate pain in the chest and abdomen without including the lower extremities. These results should point to more favorable results from chordotomy inasmuch as the section is removed from the region of the pyramidal tracts by a greater and safer distance than heretofore. Less extensive incisions are followed by lower morbidity and fewer sequelae. The differential section may prove of value in eliminating pain in the upper extremity, though we have not had such a case as yet.

CONCLUSIONS

1. The spinothalamic tract mediating the sensations of pain and temperature extends from a point about midway from the dentate ligament to the anterior roots to a point about midway from the anterior roots to the anterior median fissure. Hence a complete section should

include this region. The region extending 2 mm. anterior to the dentate ligament contains no fibers conducting sensations of pain or temperature (fig. 10 *E*).

2. As one progresses from the lower segments of the body upward, the corresponding "pain fibers" are disposed more and more anteriorly in the cord.

3. It is possible, therefore. by differential section to eliminate the sensations of pain and temperature in the chest and to retain these modalities in the lower extremities.

FUNCTIONAL CAPACITY OF THE UNDESCENDED TESTIS

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MINNEAPOLIS

I. GENERAL CONSIDERATIONS

The purpose of this paper is to present a study of the functional capacity of the undescended testis, with special reference to its potentialities for the production of spermatozoa.

While much has been written about the histologic character of the undescended testis, little attention has been paid to its function. Nearly all physicians agree that the anatomic results of surgical treatment are good, but few have inquired about the function of the organs after their placement in the scrotum. The facts recently established by research workers and clinicians in this field of endocrinology are especially significant, though as yet they are incomplete. Important discoveries are constantly clarifying physicians' views and permitting definite therapeutic advances.

The histologic aspects and the treatment of the undescended testis have been thoroughly discussed by Moore, Wangensteen, Meyer, Bevan, Cabot, Coley and others. However, a review of these subjects is given in order that there may be a better understanding of the clinical and experimental results to follow.

1. *Incidence.*—Undescended testes occur in from 0.1 per cent (Marshall) to 0.12 per cent (Monod and Terrillon) of males. Statistics on the Austrian army show that the incidence of undescended testes in every 1,000 men drafted for military service (Ziebert) was 2.2. According to the medical records of the United States War Department for the World War, there were 3.1 cases of ectopy for every 1,000 men examined. Eccles found undescended testes in 2 per cent of 48,000 cases of hernia. Bevan, Coley and Wangensteen put the incidence of retained gonad at 1 in 500.

Incomplete descent is more common on the right than on the left side. From the statistics of Berger, Hofstätter and others, the incidence of maldescent of the right testicle is equal to that of bilateral maldescent

and retention of the left testicle combined. In 20 per cent of cases of undescended testes the deformity is bilateral (Wangensteen).

2. *Causes.*—The causes of nondescent of the testis are unknown. Factors said to bring about retention of the gonad have been classified by Eccles as abnormalities of the mesorchium, of the testis and its component parts, of the gubernaculum, of the cremaster, or of the route along which the testis must pass. To these causative factors probably should be added endocrine imbalance.

McGregor concluded that ectopy of the testis can be explained on anatomic grounds. He stated that one or more of the following congenital factors are present: (1) anomaly or absence of what he called the "third inguinal ring," (2) fascial pockets and (3) fascial ridges. His careful dissections well explain the four varieties of retained testes, namely, the inguinal, the pubopenile, the perineal and the crural or femoral. Like most contemporary authors, he has questioned the gubernacular theory of descent. His own studies failed to demonstrate any subdivision of the gubernaculum, nor did they determine what causes descent.

3. *Histologic Appearances.*—Hunter concluded that the undescended testis fails to reach the scrotum because of its inherent imperfection. This cannot be wholly true, at least from an anatomic point of view, because it is impossible to distinguish histologically between a normal and a retained testis if the subject is below the age of puberty.

The histologic aspects of the retained gonad have been reviewed by a number of investigators (Eccles; Felizet and Branca; Rawling; Moore; Southam and Cooper; Pace, Wangensteen and others). Wangensteen summarized the observations as follows: The normal testis grows but slightly from birth to puberty, during which time there are few histologic changes. The undescended testis before puberty resembles the scrotal gland in weight and minute anatomic structure (table 1). With the onset of puberty, however, the normal testis shows a sharp increase in weight, which is due to the elaboration of mature epithelium and to the appearance of spermatozoa. The undescended testis exhibits these changes to a lesser degree. Wangensteen had never seen spermatozoa in the seminiferous tubules of a testis retained after puberty. This agrees with the observations of Felizet and Branca, who found that while a few undescended testes contained spermatogonia and spermatocytes, only 2 of 51 contained spermatids and none contained spermatozoa.

Southam and Cooper concluded that the farther the preadolescent testis has descended the more closely it corresponds to the normally located gland of the same age. However, a large series of cases would be necessary to verify this statement. Certainly the histologic picture of an abdominal gonad is often indistinguishable from that of an inguinal

TABLE 1.—*Gross and Microscopic Anatomy of the Descended and Undescended Testis*

Anatomy	Normal Descended Adult Testis	Undescended Adult Testis	Normal Descended Testis of Newborn	Normal Prepubertal Testis	Undescended Pubertal Testis
Macroscopic	Ovoid shape; wt., 25 Gm. each; digital fossa usually closed but may be open	Preserves contour, but smaller in proportion; body and tail may be separated from testis by mesorchium	Ovoid or bean shape; wt., 0.5 Gm.	At 15 years, wt., 11-12 Gm.; tunica albuginea and Highmore body become thicker	"Primary atrophy" (Felizet and Branca); "underdeveloped testis" (Kyrle); separation of epididymis and testis by a digital fossa; thicker tunica albuginea and Highmore body
Microscopic Seminiferous tubules	1. Several layers of epithelium	1. Germinal epithelium disappears 2. Outline of tubule may persist as hyaline ring	1. Diameter of tubules, 60 microns 2. No real lumens 3. 2-3 rows of irregular cells fill tubules	Diameter of lumen, 85-90 microns	1. Diminution in size of tubules 2. Isolation of tubule 3. Lined by epithelial cells, as normal descended testis
(a) Sertoli cells	1. Lie on basement membrane of tubules 2. Nuclei rich in chromatin 3. High fat content in cytoplasm	1. Only a single layer of epithelium consisting of Sertoli cells, may be present	1. Sertoli cells more frequent in proportion to spermatogonia	1. Definite arrangement of Sertoli cells 2. Sertoli cells less frequent in proportion to spermatogonia	1. After puberty undergoes degenerative change 2. More differentiated at 10 years
(b) Spermatogonia	1. Scattered among Sertoli cells 2. Nuclei rich in chromatin; spermatocytes 1° → spermatocytes II° → spermatids → spermatozoa	1. Absent unless just past puberty or persistence in quiescent state of nuclei of spermatogonia	1. Present singly or in groups, 1 spermatogonium to 35-40 Sertoli cells	1. Increase in number of spermatogonia, 7:20 Sertoli cells 2. Adult germinal cells become differentiated	1. Present; early, in repose later (see mitosis and spermatocytes); even spermatozoa, especially in early postpubertal period
Intertubular spaces	1. Loose	1. Increase in stroma causes tubules to be more widely separated	Delicate CT between tubules	CT between tubules contains elastic tissue	Increase of interstitial tissue, which appears in form of embryonic nucleated stroma
(a) Interstitium and (b) Interstitial cells	a. Small eccentric nuclei B. Finely granular cytoplasm c. Crystallized bodies in cytoplasm	1. Apparent but not real increase of interstitial cells	Not so prominent in fetal life	....	1. Interstitial cells are in abeyance till 10 yr. as in prepubertal descended testis

testis. The time factor is probably as important as the degree of descent in determining the histologic picture, barring any congenital malformation.

4. *Malignant Tumor of the Undescended Testis.*—Pain, torsion, hernia and malignant tumor are the most common complications of testicular maldescent. There has been much discussion about the incidence of malignant tumor of the undescended testis. Hinman reviewed 649 cases of cancer of the gonads and found undescended testes involved in 12.2 per cent. Coley, Cunningham, Odiorne and Simmons, Schischko, Lipschütz and Dean altogether reported 1,371 cases of malignant change in the male sex gland. The undescended organ was the site of malignant growth in 136, or 9.9 per cent. Since only from 0.12 to 0.2 per cent of testes are undescended, the ectopic testis appears to be involved fifty times more often than its incidence would justify. Rubaschow reviewed the cases of undescended testis reported by 21 observers and found that in 11 per cent of the whole group tumors were present, a figure in striking contrast to the 0.05 to 0.06 per cent incidence of neoplasm in the testis (Rea).

It is evident that the ectopic testis is definitely more liable to neoplasia than is the normal gland. However, the actual percentage of undescended testes undergoing malignant degeneration is another question and is the phase most commonly overlooked in the discussion of this subject. Eccles observed 859 cases of undescended testis without finding malignant tumor. Coley did not have a single case of malignant tumor in 1,357 cases of undescended testes. Kocher found only 1 case of neoplasm in 1,000 cases of maldescent. Up to 1931, MacKenzie and Ratner had never observed an instance of malignant tumor in a series of 105 cases of undescended testis. However, in 1934 they reported 3 cases in which malignant tumor occurred in retained glands. Pace found adenocarcinoma in 3 of 24 undescended testes. It should be stated, however, that the series was small, that in 1 case the diagnosis was questionable and that the degrees of malignancy were low (grade 1). Hinman stated that 3 of 155 cryptorchids had a testicular tumor—about 1 in every 50, or 2 per cent. If one checks the records of the Division of Vital Statistics at Washington, D. C., one finds that possibly 3.2 per cent of undescended testes become malignant.[1]

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1. In the registration area in 1935 there were about 1,400,000 deaths. Assuming that half of those who died were males (700,000) and considering the fact that 1 in 500 males had undescended testes, I conclude that about 1,400 men with undescended testes died in 1935. In the same year 458 men died of malignant tumor of the testis. Since malignant tumor occurs fifty times more frequently in undescended than in descended testes, $50 : 500 = x : 458$, in which x equals the number of men who died of malignant tumor of the undescended testis. Therefore, $x = 45.8$. If 45.8 of 1,400 cryptorchids died with malignant tumor of the testis, the incidence of this condition in cryptorchids was 3.2 per cent.

Haberland claimed that 0.75 per·cent of undescended testes in animals eventually show malignant tumor. Clinically the incidence of malignant change in retained testes does not seem to be higher than that in normal breasts or uteri (2 per cent). This is a contradiction of the indiscriminate castration of cryptorchids for fear of malignant change.

When one considers the low incidence of malignant degeneration in undescended testes, as well as the fact that in 20 per cent of cases of retained testes the condition is bilateral and the generally poor results in the treatment of testicular neoplasms, one must conclude that the procedure of choice in the treatment of the ectopic gland is orchiopexy. That orchiopexy per se does not protect against malignant developments has been mentioned in the reviews of Wangensteen and Rea, as there are instances in which malignant tumor later occurred in testes on which the operation had been done. However, this and the other evidence cited would tend to show that it is not so much the position as "the biophysical and chemical factors involved in the growth of tissue" that plays the important role in neoplasia of the undescended gland (Hinman).[2]

5. *Internal Secretion of the Retained Testis.*—The existence of a male sex hormone, androgen, has been recognized for a long time. The interstitial cells, first described by Leydig in 850, were regarded as its source by Bouin and Ancel in 1903. The hormone is thought by most investigators to be unrelated to spermatogenesis. However, since some germinal epithelium usually persists in most conditions of aspermia, as in undescended or irradiated testis, Oslund stated that it has not been determined whether the germinal epithelium, the interstitial cells or both produce the hormone. Some workers have regarded the interstitial cells as secretory, while others have concluded that they are no more than modified connective tissue cells (Moore).

The effects of deprivation of this hormone, as by castration, are well known. As the effects of its removal are immediate, none of the substance appears to be stored in the body. Deficiency during the development of the organism will affect the accessory and secondary organs of sex; deficiency after development will affect their normal activity (Moore). The effect of castration on the epididymis, the vas deferens, the seminal vesicle and the prostate is so constant that Moore has used it as a "testis-hormone indicator." The high columnar epithelium of the seminal vesicle of the rat changes considerably within twenty days after castration. The subcutaneous injection of the purified lipoid extract of fresh bull testis restores the vesicle of a castrated rat.

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2. Most of the foregoing data and statistics are mere rationalizations, however. The whole problem will be settled only by more records of the number of patientwith undescended testes dying of a malignant neoplasm of the testis.

Guinea pigs within three months after castration lose the reflex of ejaculation on electrical stimulation of the brain, but it reappears within two weeks after the subcutaneous injection of fat-soluble androgenic substance. Capons have also been used in tests for the presence of androgen; in fact, the first testicular graft, by Berthold (1849), was of this type. If androgen is present, castrated chickens, even females, will grow combs, wattles and ear lobes. The urine of normal men contains a substance which promotes growth of combs in capons (see reviews of Moore, Koch and Hinman).

It has been proved by the capon comb test that androgen is present in cases of single and bilateral testicular maldescent (Koch; Webster). Clinical evidence of the presence of this hormone in cryptorchids, as shown by the development of the secondary sexual characteristics, has been recognized for some time. Pratt, Moore, Hinman and Meyer stated that most patients with undescended testes exhibit normal physical and mental development except for occasional psychic disturbances of the sexual power. All but 1 of the 20 adults with bilateral cryptorchidism seen at this clinic have had normal secondary sex characters. The exception had Fröhlich's syndrome.

Lipschütz stated that one sixteenth of the normal testis suffices to permit normal development of the secondary sex characters in the rabbit and the guinea pig. Judging from the small size of the gonads occasionally seen in otherwise normal cryptorchids, little testicular tissue seems to be needed to carry on this function in man.

Whether the undescended or the normal testis internally secretes more than one hormone is not definitely known, but the fact that the undescended testis has an internal secretion has been a strong argument for its conservative treatment (orchiopexy) rather than its removal (Meyer; Lotheissen).

6. *External Secretion of the Retained Testis.*—(a) Spermatogenesis in the undescended or incompletely descended testis. The imperfectly descended testis is often aspermatic. This is thought to be due to the influence of the higher body temperature of its abnormal surroundings on the germinal epithelium (Piana; Crew; Moore; Fukui) and also the pressure atrophy. Most experimental evidence seems to show that the undescended testis will develop normally when replaced in the scrotum. If it is too far degenerated, mature germinal epithelium will not be produced subsequent to fixation in the scrotum.

In experimental procedure a normal testis is brought up into the abdomen, allowed to degenerate, replaced in the scrotum and then seen to regenerate. It may be questioned to what extent this regeneration will occur in the naturally cryptorchid gland after orchiopexy, since the potentialities of such a gland may be entirely different from those of the normal gonad. Wangensteen has noted that restoration of the mature

germinal epithelium does not occur to the same extent after orchiopexy as after the return to the scrotum of a normal testis previously placed in the abdomen by operation.

(b) Fertility of cryptorchids. Griffiths concluded that the undescended testis is incapable of producing spermatozoa and doubted the authenticity of reports of fertility in cases in which the condition was bilateral. From a review of the literature, however, it seems clear that spermatogenesis may occur in cryptorchids. Unfortunately the details of most of the reported cases are so incomplete that one wonders whether the authors did not state impressions or prejudices as facts.

Cooper taught that patients with bilateral failure of testicular descent are like castrates. A medical student with bilateral cryptorchidism consulted him and on hearing of the probable outcome of his anomaly committed suicide. Cooper examined his testes and found spermatozoa in each. Uffreduzzi stated that 10 per cent of cryptorchids exhibit spermatozoa. Marechal found 50 cases of bilateral cryptorchidism in which examination of the testis or of the semen revealed spermatogenesis. Rawling found little if any impairment of spermatogenesis in 10 of 27 undescended testes and stated that organs situated in the inguinal, pubic and pubosacral regions exhibit spermatogenesis in from 40 to 50 per cent of persons up to 30 to 40 years. Vidal and Burghard concluded that the majority of abdominally retained testes are capable of spermatogenesis. Meyer, in a review of the literature, quoted 19 authors who stated that the cryptorchid testis is capable of producing spermatozoa and 13 who held the opposite view. In the majority of instances in which spermatozoa have been demonstrated in the undescended testis the patient has been young.

Odiorne and Simmons, Eccles, Levin and others have reported the cases of patients with bilateral abdominal cryptorchidism who apparently became fathers. Eccles stated that there are few instances of fertility in the presence of double inguinal arrest. Why abdominal retention should be more conducive to fertility is not clear.

Since Hobday stated that stud horses with abdominal testes are always sterile, the statement that abdominal retention is less inimical to spermatogenesis than is inguinal retention is probably untrue.

At the University of Minnesota Hospitals ejaculation tests have been done on 4 patients with bilateral inguinal testes and 2 with abdominal gonads. These patients have never had any treatment for their anomaly. Their ages varied from 21 to 28 years. Spermatozoa were absent from the semen of 3 with inguinal and from 1 with abdominal testes. A patient aged 24 years, with abdominally retained testes, had in the semen on one occasion only scattered sperm (1 to 3 per high power field), and these were nonmotile; he was married and

was reputed to be the father of a child. Another patient, also 24 years of age, with bilateral inguinal testes, produced motile sperm on two occasions; first there were only 4 to 5 per high power field, but at the next examination there were 1,500,000 per cubic centimeter. He was married and claimed to be the father of a child; his wife was again pregnant at the time of his last examination. Paternity tests have not been performed in either case.

Whether cryptorchids are potentially or absolutely fertile is an important question. Macomber and Saunders stated that the semen of the normal male contains between 100,000,000 and 120,000,000 actively motile spermatozoa per cubic centimeter. Rubin estimated that as many as 400,000,000 per cubic centimeter may be present. The normal count for the same person varies with illness, age, exercise, diet, mental and physical fatigue, alcoholism, endocrine imbalance and frequency of sexual intercourse. It has been estimated that normally the count does not go below 50,000,000. Twenty-five million spermatozoa per cubic centimeter have been considered but not proved to be the minimal number compatible with fertility, as approximately this number are thought to be destroyed by the vaginal secretions (Macomber and Saunders; Belding).

Macomber and Saunders reported fertility in persons with counts lower than 25,000,000. MacCollum reported his experience with 2 men each of whom had been operated on for unilateral undescended testis; the counts were 16,000,000 and 26,000,000, respectively. Both men were fathers. While repeated tests might have given counts high enough to account for the paternity, it is also possible that the figures cited as necessary for fertility are too high; certainly the number of spermatozoa is only one of the factors involved in fertilization. The nature of the associated secretions in the male and female is probably as important. I have reported an instance of paternity with a sperm count of 1,500,000. the lowest recorded in the available literature. While it is impossible actually to prove or disprove paternity, the fact that the numbers of spermatozoa supposed necessary for fertility are only estimates and the fact that only one spermatozoon is necessary for fertilization make it probable that fertility may exist in patients with sperm counts below the present accepted standards. Moreover, studies of the head, neck and tail of the sperm show that from 8 to 10 per cent may show variations in size and shape. Fertility is thought to be greatly impaired if the proportion of abnormal forms reaches 25 per cent.

To draw valid conclusions as to the fertility of bilateral cryptorchids is impossible, because too few observations have been made. However, it seems permissible to conclude that some males with bilateral cryptorchidism have not only potential fertility but also presumptive evidence

of absolute fecundity (2 of 6 of my patients). All such patients whom I have observed have been young; whether fertility exists in older patients is unknown.

7. *Treatment.*—(*a*) Spontaneous descent. Hofstätter stated that in 600 male newborn children 96 per cent of the testes were in the scrotum. In eight to ten days nearly all the testes were in the scrotum or slipped out of the external ring easily. If the testis fails to reach the scrotum at the end of the first year of life, it will be a rare event if it ever does so by its own initiative (Hofstätter). At the University Hospitals no spontaneous complete descent has been noted in a series of 100 imperfectly descended testes in patients aged 2 to 79 years. To be sure, there are several reports of late descent in the literature (Bühlmann; Mayor; Harris; Drake). The most interesting of these studies is that of Drake. He found that 11 of 260 boys, aged 9 to 19 years, had undescended testes (incidence, 4.2 per cent); in 4 the retained gonad was on the right side, in 6 it was on the left, and in 1 the condition was bilateral. Drake observed these boys for a period of years and found that 10 of the 12 testes descended spontaneously. If most undescended testes descend of their own accord, as Drake inferred, it is difficult to explain the incidence of 3.1 cases of ectopy per thousand men according to the draft statistics. Also, since the incidence is about twenty times the normal incidence (0.2 per cent), it is possible that the condition in a number of his cases could be classified as physiologic ectopy.

By physiologic ectopy is meant the condition in which one finds a normally descended testis with a very short or active cremasteric muscle which pulls the gonad into an inguinal or a high scrotal position. This condition, also known as ectopy en retour, has been little appreciated by most investigators. From the point of view of therapy, it is as important to differentiate it from true maldescent of the testis as it is to differentiate testicular maldescent from hernia, from benign and malignant tumors in this region or from adenitis. MacCollum noted 21 instances of physiologic ectopy in 336 cases of cryptorchidism. Of 16 patients referred to Hamilton and Hubert, only 6 were actually cryptorchids; 10 were pseudocryptorchids. Stefko in 1924 reported a high incidence (27 per cent) of inguinal testes in starving children. This he attributed to shortness of the cremaster, caused by starvation, in which an unequal growth of muscles of the abdominal wall occurs. Hofstätter described a group of 8 to 10 year old boys who could luxate their testes, pushing them into the inguinal canal and even into the abdominal cavity. On one occasion one of these boys could not replace a testicle which he had pushed above the penis, and only with difficulty could it be replaced by a physician. Bevan stated that one fourth of the

patients with retained testes referred to him do not have undescended testes, for when a finger is run down the inguinal region the testicle can be pushed into the scrotum.

To differentiate physiologic ectopy from testicular retention the following criteria may be helpful: 1. In physiologic ectopy the extremely short or active cremaster may be seen to contract. 2. The patient may state that at one time the testis was in the scrotum. 3. Physiologic ectopy is not associated with hernia as frequently as undescended testis. 4. In physiologic ectopy the testicle can be brought into the scrotum by manual traction, but when the traction is released the testicle recedes to its original position. 5. The scrotum in such cases is better developed than in cases of cryptorchidism. 6. In children with strong cremasteric reflexes the testis does not usually enter the inguinal canal but lies under cover of the loose fatty tissue which covers the front of the pubes. If the examiner palpates the region immediately below the external ring, the cord can be picked up by the fingers. When this is traced the testis will be found (Fraser). 7. If relaxation of the cremasteric and other muscles is obtained by a general method of approach and by direct application of heat to the groin, scrotum and perineum (the patient lying with his legs apart) a differentiation between pseudocryptorchidism and true cryptorchidism can be made (Hamilton and Hubert).

A sharp distinction cannot always be made between these two entities, but the history and multiple observations by different examiners will aid in the diagnosis. At the University Hospitals at least three examiners check every diagnosis of undescended testis. Physiologic ectopy may be considered to vary from true maldescent only in degree, but certainly differentiation should be made in tabulating any results of treatment.

The ultimate fate of physiologically ectopic testes has not been definitely ascertained. MacCollum gave one to understand that if such testes can be brought into the scrotum they will eventually descend of their own accord. Bevan also concluded that at puberty, when the testes enlarge, they descend into the scrotum and develop normally. Wangensteen has brought to my attention several cases which he has followed personally. Nearly all the patients had been referred for orchiopexy, but they were not operated on when the real condition was appreciated. Of 3 boys in one family, 2 had physiologically ectopic testes which descended into the scrotum at puberty and have remained there to the present time. At a recent examination the testes of both boys were normal in size, shape and position. The other boy, aged 11 years, had an inguinally retained left, testis. Another case of physiologic ectopy has been followed; when the patient was 12 years old the right testis descended into the scrotum and has remained there, but it is about half the size of its scrotal fellow.

(*b*) Surgical treatment. The surgical treatment of the undescended testis is removal, abdominal reposition or scrotal fixation (orchiopexy). Castration is justified only in certain cases of unilateral undescended testis: (1) if the patient is old and has a very atrophic testis or a large inguinal hernia, (2) if the testis is painful or (3) if the presence of a malignant tumor is suspected. Too often castration is performed because it is an easier procedure than scrotal fixation. However, it is surprising how much the cord can be lengthened by patiently separating the testis from the vaginal process, freeing the vessels and vas deferens in the retroperitoneal space even as far as the renal pedicle and separating the fascial coverings of the cord. Cutting the blood vessels of the cord to give length is to be condemned, as Mixter and MacCollum found that every patient so treated showed complete atrophy of the testes when observed from ten to twenty years later. If an inguinal testis cannot be made to reach the scrotum, abdominal reposition is preferable to castration and may be the only elective procedure for the young male with bilateral cryptorchidism.

In orchiopexy one combines the freeing of the cord with fixation of the testicle in the scrotum. Since Rosenmerkel's orchiopexy of more than one hundred years ago, numerous procedures to anchor the testis in the scrotum have been devised (see Hofstätter's outline). Over 40 operations have been described (Wolfson and Turkeltaub). The most recent ones are of the Keetley-Torek type. From many reports (Burdick and Coley; McKenna and Ewert; Ada; Gobell; Cabot and Nesbit; Tyrrell; Meyer; Eisenstaedt; Wangensteen; Newell; Wolfson and Turkeltaub and others) it is to be inferred that good anatomic results (in size, position and cosmetic effect) are obtained in most cases, even with various technics. For the past few years at the University Hospitals Wangensteen's modification of the Keetley-Torek operation has been used with uniformly good results.

In the Keetley-Torek operation the spermatic cord is freed until it is of sufficient length to allow the testicle to reach the bottom of the scrotum. The skin of the thigh is sutured to the skin of the scrotum; the testicle itself is sutured to the fascia lata of the thigh, and the wound in the scrotum is closed over the testicle. The testicle is thus kept at enough stretch so that it will remain low in the scrotum after the second stage is performed. It is important that there be no undue tension. At the second stage the scrotum is separated from the thigh and the testicle from the fascia lata, and the scrotum is closed again over the gonad. In Wangensteen's operation a cutaneous juncture between the thigh and the scrotum is made, and the testis is anchored by means of sutures which are placed in the tunica albuginea, brought down through the tunica vaginalia communis and fastened to the fascia of the thigh. The important difference in this operation is that while

fastened to the thigh the testicle is still in the scrotum. The first stage is not only more physiologic than in the original Keetley-Torek procedure but at the second stage, the scrotal-crural detachment is performed more easily and simply.

From an anatomic and from a physiologic point of view, orchiopexy is the procedure of choice in the surgical treatment of the undescended testis. It is important that the testis after orchiopexy lie free in the bottom of the scrotum and be movable. If one cannot get the testicle to the lowest portion of the scrotum, a high scrotal position is better than an inguinal one. If necessary, the testicle may be brought from its ectopic position to the scrotum in stages. Whether inguinal or abdominal reposition is the better is questionable, except that one can observe a testis better in the inguinal region. If the inguinally retained testis is painful and if conservative measures give no relief, orchidectomy may be indicated, as such a testis will probably be just as painful if placed in the abdomen. For older men, orchiopexy may be performed more for the cosmetic result than for the functional potentialities.

(*c*) Endocrine therapy—rationale. The researches of Evans, Engle, Aschheim and Zondek, Allen, Doisy and others are largely responsible for physicians' ideas regarding the hypophysial-gonadal relationship, as well as the rationale of endocrine therapy for cryptorchidism.

Allen has reviewed the effect of estrogen on the testis. While few distinctly harmful effects on the testis of the adult male follow the injection of moderate doses of estrone (theelin), degenerative changes in mature testes have been described as following the administration of large doses. In the immature male, however, it is possible to inhibit the normal growth of the spermatogenic tissue with relatively small amounts of estrogen. The testes remain infantile, sperm is not developed, and descent of the gonads into the scrotum is inhibited. The thymus gland does not undergo its usual involution. The accessory genital organs remain undeveloped. Moore concluded that these inhibitory effects may be explained by a depressing effect of the injected estrogenic substance on the anterior lobe of the pituitary gland as far as its production of a secretion essential to the normal growth and function of the testis is concerned. Burrows found that estrone tends to inhibit the descent of the testes, to prevent the testes from maturing and to induce hernia only if the testes are nearly or quite mature.

The effect of pituitary extracts on the testis is different from that of estrogen. In 1921 Engle isolated from fresh bovine anterior lobe the growth hormone of the pituitary gland. It was noted, however, that besides failure of growth, there was failure of genital development in children hypophysectomized because of a pituitary tumor and that similar retrogressive changes occurred in the genital system of adults.

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The independence of the gonadotropic and growth factors of the anterior lobe of the pituitary was proved by Zondek and also by Smith, who in 1926 simultaneously detected the gonadotropic hormone of the hypophysis. They found that subcutaneous implants of anterior lobe tissue into immature rats provoked sexual maturity in these animals in from three to five days.

A more convenient source of gonadotropic substances was discovered by Aschheim and Zondek in the urine of pregnant women. It is known that estrogen is found in large amounts in the blood and urine during pregnancy and also in the placenta. It has been known for some time that the hypophysis undergoes hypertrophy during pregnancy. It was rationalized, therefore, that during gestation there would be increased secretion and elimination of the anterior pituitary gonadotropic hormone. It was subsequently found that gonadotropic substance appeared in the urine during pregnancy in large amounts and much earlier than estrogen —as early as the first three weeks of gestation, affording a diagnostic test for pregnancy (Aschheim-Zondek test).

The estrogenic substance in the urine can be separated from the gonadotropic because of the greater solubility of the former in organic solvents. Whether the gonadotropic substance in the urine is identical with the pituitary gonad-stimulating hormone has been questioned (Evans; Collip and his co-workers; Fevold and Hisaw; Zondek).

The action of the various extracts from the anterior lobe of the pituitary gland and of the urine of pregnant women has been studied in both mature and immature male animals, chiefly rats, mice and monkeys. Engle reviewed the results obtained by most of the recent workers in this field. It was noted that while injections of whole urine of pregnant women caused hypertrophy of the accessory sex apparatus, no constant change in the size of the testis occurred, and while the interstitial mass was increased, there was no acceleration of spermatogenesis. The only uniformity of agreement among investigators on the response to extracts of the anterior lobe or to the gonadotropic substance from the urine of pregnant women is that premature development of spermatozoa has not been demonstrated and that animals which have been treated do not mate. Thus the acceleration of development and even maturation of the genital system should not be considered synonymous with sexual maturity (Moore). Engle summarized the data acquired through the study of a series of animals, both rats and monkeys, as follows: 1. The testicular weight of animals treated with either concentrated urine of pregnant women or with pyridine extracts of sheep glands is considerably increased. 2. The increase in the interstitial mass after the use of anterior pituitary extract is slightly greater than in the untreated control, but after the use of concentrated urine

of pregnant women it is greatly increased. 3. Neither of these degrees of change has been noted to follow fresh implants. 4. The failure to induce acceleration in spermatogenesis is uniform with the findings after implantation, although the size of the tubules is greater than in the controls or the rats receiving implants.

Engle also found that injections of extracts of urine from pregnant women and water-soluble extracts of the anterior lobe of the pituitary gland produced descent of the testes in 10 immature macaques. Normally the male macaque exhibits at birth turgescence of the scrotum and descended testes. Shortly after birth the testes ascend into the inguinal ring, while the scrotum regresses until it becomes a flattened fold of skin between the thighs. Not until the third to the fifth years do the testes descend again permanently, at which time the scrotum becomes fully formed (Wislocki). In the monkeys treated by Engle the testes grew, and during the course of treatment the scrotum increased in size even before the testes had descended into it. The same author noted the similarity between the scrotal response in monkeys and that in newborn human children. Since in the human male the testes are descended at birth and in the human female the gonadotropic principle is in the circulation throughout the period of gestation, Engle postulated that the hormone is involved in the descent of the testes in the human male.

Aberle and Jenkins injected about 2,575 rat units of the gonadotropic principle from the urine of pregnant women into each of 6 monkeys. The testes enlarged, but only a single testis descended to the lower part of the scrotum. Biopsy of the testes showed tubular enlargement and increase in interstitial tissue but no mature spermatozoa. Grossly, there was shortness of the fascia surrounding the vas deferens and spermatic vessels, which was believed to be responsible for lack of complete descent. They stated that Engle used monkeys that were heavier and therefore probably older and more mature. Unfortunately, the amount of gonadotropic substance given by Engle was not stated. According to Aberle and Jenkins, identical amounts of the gonadotropic substance from the urine caused various degrees of hypertrophy in the prostate, seminal vesicle and testes of immature monkeys.

Smith and Leonard, who used gonadotropic substance from the urine of pregnant women (antuitrin-S) in hypophysectomized rats, stated that spermatids and even sperm may be found, though none was present at the beginning of treatment. When injections were begun at the time of hypophysectomy the regression in the weight of the testes was slowed, and enlargement sometimes was found. Atrophy of the tubules was retarded, and mature spermatozoa continued to be present longer than in the hypophysectomized litter mates. Smith and Leonard concluded that in pituitary insufficiency injections of urine from pregnant women might have a beneficial effect on spermatogenesis.

That the testes influence the activity of the pituitary gland has been shown by many investigators. Severinghaus, Engle and Smith, in their review of the literature, related the histologic changes in the anterior lobe of the hypophysis following castration in the male or female. One is impressed, however, with the fact that the changes are not identical in all species. The hypophysis of the castrated rat shows a marked increase in basophils, while the same organ in the castrated man, horse, ox, pig, cat, dog, guinea pig, rabbit or domestic fowl is said to show an increase in eosinophils. Nelson found that as the testes of the experimentally cryptorchid rat underwent degenerative changes the hypophysis also exhibited changes which were similar to those found after castration. The injection of gonadotropic substance from the urine of pregnant women (antuitrin-S) into these animals resulted in stimulation and restoration of the seminal vesicles and of the prostate, while the hypophysis showed a disappearance of castration cells. There was no change in the epithelium of the seminiferous tubules, but the interstitial tissue of the testis showed marked stimulation. The treatment of a series of castrated rats with gonadotropic factor extracted from the urine of pregnant women resulted in no change in the hypophysis or in the accessory sex glands. Nelson concluded that the testis plays an intermediary role in the influence exerted on the pituitary and accessory sex glands.

Evans and Simpson, and Collip, Selye, Anderson and Thomson, working with laboratory animals, have shown that the combined use of an alkaline extract of the anterior lobe of the pituitary gland and gonadotropic substance from the urine is more effective than the use of either alone, the former activating or enhancing the gonadotropic principle by its synergistic action. Smith and Leonard, Evans, Pencharz and Simpson have shown that a pituitary extract from the urine of pregnant women may produce stimulation of the germinal epithelium of the testes, but maximal or complete results were obtained in their work by a combination of the pituitary extract and gonadotropic substance from the urine of pregnant women. The anterior pituitary substance does not seem to bring about complete spermatogenic maturation of the testis, as the work of Engle, Rubinstein, Aberle and Jenkins has shown. The studies of Schockaert, Brosius and Schaefer, and Kraus seemed to suggest this possibility, but it was not conclusively proved that their experimental subjects did not display this function before treatment.

There are several series of human undescended testes which have been treated with the gonadotropic substance from the urine of pregnant women. A report of these cases and the results of treatment in similar cases at the University Hospitals will be discussed later.

8. *Results of Treatment.*—(*a*) Function after glandular therapy. There are no controlled reports in the literature in which an aspermatic undescended testis is said to have shown active spermatozoa after treatment with the gonadotropic substances from the urine of pregnant women. The results following the injection of serum from pregnant mares will be discussed later. If there is a potentially active germinal epithelium in the undescended testis, it is theoretically possible that descent induced by the gonadotropic substances mentioned might result indirectly in spermatogenesis as a result of better (scrotal) position.

(*b*) Function after surgical treatment. In the available literature there are only 2 series of cases in which the functional results following orchiopexy have been recorded. In 1935 Wangensteen reported that, of 6 patients with bilateral failure of descent, spermatozoa were found in the semen of 4 after orchiopexy. In no case was the number of spermatozoa per cubic centimeter as high as in the normal person. MacCollum found that 82 per cent of 22 patients with bilateral undescended testis operated on at the Children's Hospital, Boston, were fertile after operation. When one considers that only about 10 per cent of untreated cryptorchids show spermatogenesis (Uffreduzzi), the value of operative treatment is apparent. It would be more real, however, if one knew (1) how long an untreated cryptorchid may remain fertile, (2) the sperm count before and after orchiopexy and (3) the histologic appearance of the testis before and many months after scrotal anchorage (see Wangensteen's case).

II. SCOPE OF THIS STUDY

The purpose of this study is to determine how closely the functions of the undescended testis approach those of the normally descended gland, both before and after fixation in the scrotum.

Although orchiopexy has been performed for more than a century, few investigators have inquired whether the undescended testis has any function, or, if function exists, whether it can be maintained or improved by scrotal fixation. From the evidence in the literature it seems established that undescended testes have an internal secretion and occasionally possess an external secretion sufficient for potential, if not absolute, fertility.

Knowledge of the functional capacity of the undescended testis is important as a basis for rational treatment. It is generally agreed that in most mammals maldescent of the testis, whether congenital or experimental, progresses to atrophy after puberty. Conclusions concerning the results of treatment have been based on both clinical and experimental cryptorchidism. However, there are limitations to the clinical investigation of a problem of this type. Also, it may be questioned to what extent one is justified in drawing conclusions from researches based on

experimentally cryptorchid subjects in which the potentialities of the normal gland were originally present. As has been mentioned, the potentialities of the congenitally undescended gland may be entirely different.

III. TESTICULAR MATERIAL INVESTIGATED

In the experimental study of this problem only naturally cryptorchid animals, chiefly the dog and the pig, were used, unless otherwise specified. In these animals cryptorchidism is not infrequent. While working in the experimental laboratory of the department of physiology of the University of Illinois Medical School, I noted 7 instances of undescended testis (in 2, bilateral) in 200 dogs. At the stockyards of Armour and Company, South St. Paul, Minn., during one of the morning "kills," 4 instances of retained testes were noted in approximately 2,000 pigs. In this investigation the naturally occurring cryptorchid testes of 26 pigs and 15 dogs were studied. In the operative procedures, pentobarbital sodium (35 mg. per kilogram of body weight), injected intraperitoneally, and drop ether were used as the anesthetics. Sterile precautions were used in the surgical operations.

IV. OBSERVATIONS IN ANIMALS AND MAN, WITH PERTINENT CITATIONS FROM THE LITERATURE.

1. *Histologic Appearance of the Undescended Testis.*—In this laboratory congenitally undescended testes have been studied histologically in the pig, dog, horse and bull. The microscopic appearance of the retained testis in each of these animals is similar to that in man and is comparable to that in cases of experimental cryptorchidism (table 1 and figs 1 and 2). The testes are ordinarily smaller than normal, their tunics are usually thicker, and the cut sections are darker and more fibrous. They contain seminiferous tubules in which only Sertoli cells may be visible. Some cells of the germinal line are found, but there is never a complete germinal epithelium if the testes have been entirely confined to the abdomen. Testes located in the inguinal region or the upper part of the scrotum may occasionally contain spermatozoa, but this is rare in the adult animal, according to Moore.

In this study the microscopic sections never showed spermatozoa in the lumens of the seminiferous tubules of congenitally abdominal or inguinal testes whether these were from adult man, pig or dog. Botschi described the appearance of congenital undescended testes in the pig, horse, dog and cat. He found that in these animals the greater number of retained testes are aspermatic and that even spermatocytes are seldom found. Wangensteen concluded that the germinal epithelium is better maintained in the undescended gonad of the horse than in that of man, pig, dog or bull.

In most animals the empty tubules are more widely separated in the undescended than in the scrotal testis. The amount of interstitial tissue varies in different animals. The interstitial mass of the cryptorchid

boar is so prominent that Bouin and Ancel designated such tissue the "interstitial gland." The interstitial cells are less evident in the ram (Moore).

2. *Spermatozoa in Smears and Sections of Descended and Undescended Testes.*—(a) Pigs. The following study concerns abdominal
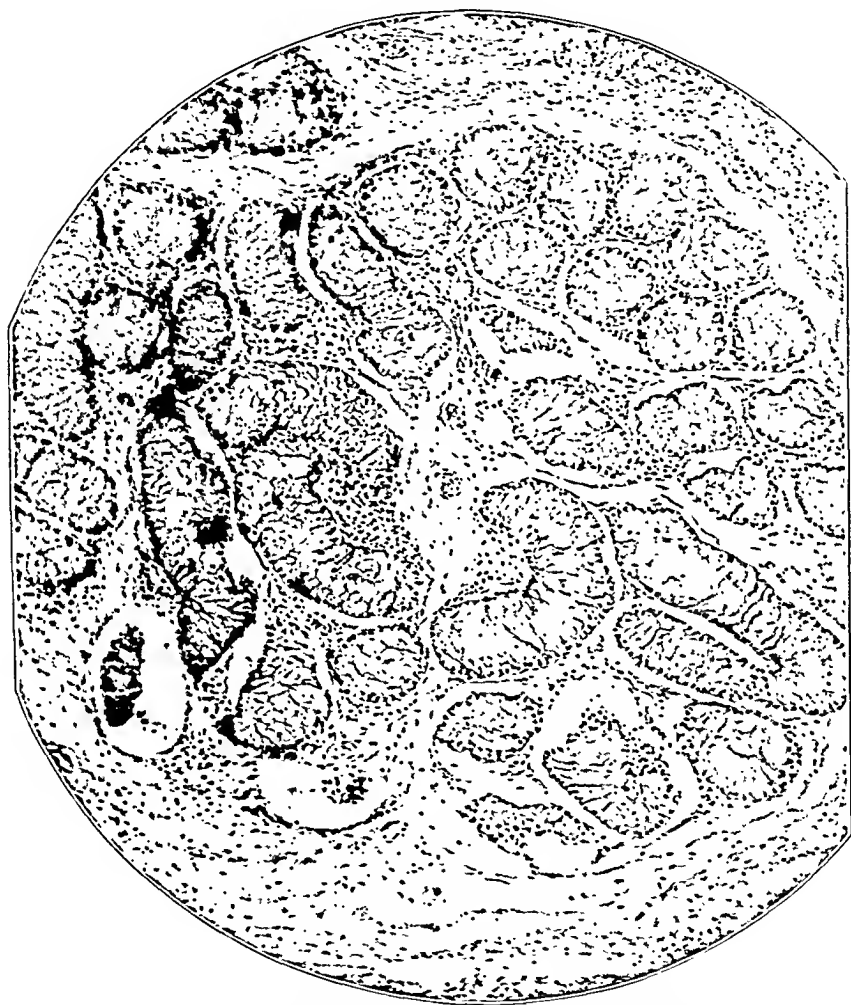
Fig. 1.—Section of a congenitally undescended canine testis ($\times 700$). Note the tubular degeneration, the increase in interstitial tissue and the lack of spermatozoa in the lumens of the tubules.

testes in 11 full grown pigs, obtained through the courtesy of Armour and Company, South St. Paul, Minn. Smears were made from cut sections of the testis, epididymis. vas deferens and seminal vesicles and were stained with iron hematoxylin and methylene blue. Microscopic

sections were then made from each of these organs and from the prostate and were stained with hematoxylin and eosin. Both smears and sections were searched for spermatozoa, and the germinal epithelium was scrutinized.
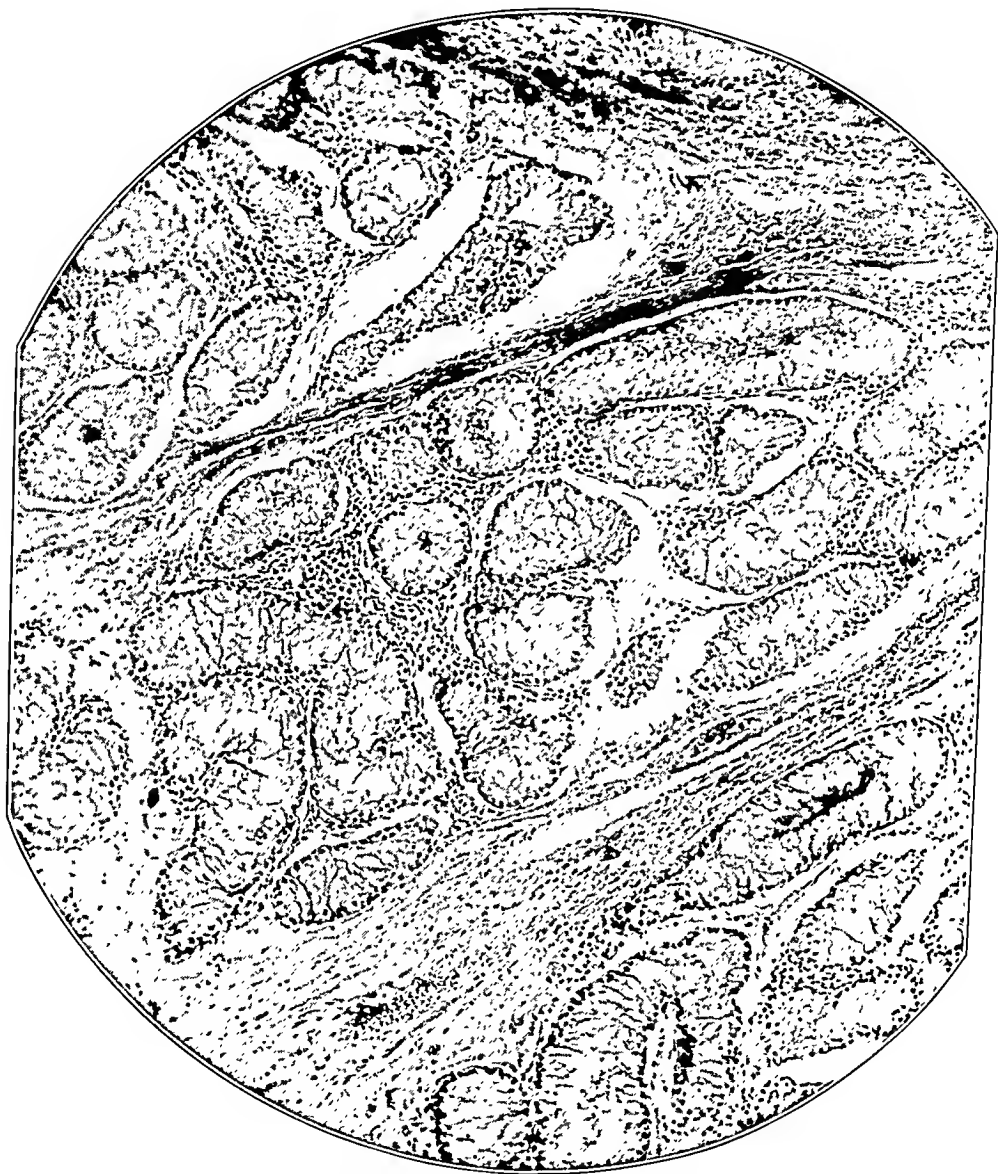
Fig. 2.—Section of the inguinally retained left testis (× 700) of an adult dog (dog 1, table 1) after scrotal fixation for three months. Degeneration and atrophy are still apparent; there is no evidence of germinal maturation. There is little difference between this treated testis and that shown in figure 1.

The gonads in every case revealed the usual degenerative changes. In none was there a mature germinal epithelium. There was marked increase in the interstitial tissue. However, smears made from cut sections of the testes revealed spermatozoa in 6.

Although the smears of the epididymis and seminal vesicles in 2 instances showed spermatozoa while the microscopic sections did not, this was probably due to the manner of preparing the slides. As controls, sections and smears were made of the testis, epididymis, vas deferens and seminal vesicles of 3 adult boars. In all instances spermatozoa were seen in sections of the testis and epididymis and in smears of the testis, epididymis, vas deferens and seminal vesicles.

The finding of spermatozoa in abdominal testes of pigs raises the question of fertility. Hobday represented most veterinarians as considering animals with abdominally retained testes sterile but reported finding spermatozoa in 2 of 14 abdominal testes and in 5 of 11 inguinal gonads from horses. In the present study smears of the cut surfaces of testes from 11 cryptorchid pigs yielded spermatozoa in 6.

From the foregoing data it would seem that in some of the lower animals potential fertility may exist for a longer period than is generally believed.

(*b*) Man. A similar study was carried out with the normally descended human testis. At postmortem examination, smears and sections were made from the cut surface of the testis and occasionally from the epididymis, vas deferens and seminal vesicle. The former were stained with methylene blue and the latter with hematoxylin and eosin. In 18 consecutive autopsies on male patients smears and sections were made of 32 adult descended testes; the smears of 6 of these testes contained spermatozoa, but the sections did not. Histologically the testes often appeared disorganized, probably because of the infection from which many of the patients died. That illness may have an unfavorable result on spermatogenesis has been stressed by Wangensteen.

This and the studies on the pig indicate that smears from cut surfaces of the testis or seminal vesicle are a far more reliable index of the presence or absence of spermatozoa than are histologic sections of the testis. It is interesting that such poor-appearing germinal epithelium may elaborate spermatozoa. While some areas of the gonad may appear more nearly normal than others, my studies of cryptorchid pigs show that the germinal epithelium is never as mature as that in the normal gland.

3. *Hypophysis of the Naturally Cryptorchid Pig.*—It has been previously mentioned that in experimental cryptorchidism the hypophysis undergoes changes similar to those seen after castration. Fortunately, hypophyses were obtained in 5 cases of undescended testes of adult pigs. In 2 cases the maldescent was bilateral. The sections were fixed in Zenker's solution and were stained by Mallory's modification of the azocarmine stain. Dr. A. T. Rasmussen of the department of neurology of the University of Minnesota School of Medicine reviewed the slides

and agreed with me that there is no evidence of castration cells (vacuolated basophils) in the pituitary gland of any of these 5 animals. The histologic character of these glands as to type and number of cells was by him considered normal. In each of the 3 cases of unilaterally retained testes the other testis had been previously removed, presumably by castration. Sections of these 7 undescended testes (2 bilateral, 3 unilateral) revealed no mature germinal epithelium. Smears of the testes in the two cases of bilateral maldescent failed to show spermatozoa. It seems logical to conclude that either (1) there was some other endocrine balance which kept the hypophysis morphologically normal or (2) the changes seen in the hypophysis in experimental cryptorchids are not the same as those seen in cases of naturally occurring undescended testes. In this connection Dr. Rasmussen has called my attention to a recent autopsy performed at Ancker Hospital, St. Paul, Minn. The patient was a man 34 years of age, who had died of pulmonary tuberculosis. The testes were scrotal but underdeveloped and hypoplastic, measuring about 1 cm. in diameter. Microscopic examination revealed an atrophic germinal epithelium, yet the hypophysis in this case was normal histologically. The prostate was also of normal size.

From the foregoing data one begins to wonder how necessary and direct the hypophysial-gonadal relation always is. Also it may be questioned what benefit would be derived in such a case from the use of the gonadotropic substance from the urine of pregnant women in the treatment of undescended testes.

4. *Tissue Culture of Undescended and Descended Testes of Man and Dog.*—Theoretically, the best way to study the histologic potentialities of any organ is by tissue culture. In the available literature there is no report of tissue culture of the naturally undescended testis. Goldschmidt, Fischer, Champy and Esaki have reported the results of culture of testicular tissue of various species. Esaki studied cultures of testicular tissues from normal guinea pigs and rabbits and from animals in which cryptorchidism had been produced experimentally. Levi in 1934 gave the most complete review of the subject to date.

The various studies seem to indicate that the epithelial nature of testicular cells is less definite in tissue culture than that of the germinal cells of the ovary. In cultures of the testes of the rabbit, the Sertoli cells change into large round cells which will phagocytose carmine and the germinal elements. Esaki found that the Sertoli cells in cultures of testes from rabbits with experimentally produced cryptorchidism became fibroblastic. In fact, dedifferentiation to fibroblastic tissue took place readily. The interstitial cells are not phagocytic and must be sharply differentiated from the histiocytes. They are transformation products of undifferentiated mesenchyme and under favorable conditions can change into fibroblasts. The difficulties and limitations of working with

a greatly differentiated tissue like that of the testis are apparent to any one who has made tissue cultures. However, it was thought that a comparison of the line of development in cultures of descended and of naturally ectopic testes might be helpful in elucidating the potentialities of these two types of organ.

Through the cooperation of Dr. Joseph King of the department of physiology at the University of Minnesota School of Medicine, cultures were made of tissues from 3 undescended human testes, 4 descended human testes, 1 naturally undescended canine testis, 2 descended canine testes and 3 normal, descended testes of rabbits. These tissues had been removed under sterile precautions. In each of 2 of the cases of undescended human testes a small slice of gonad was removed for tissue culture at orchiopexy. In the third case an orchidectomy was performed because of the small size of the testes and the large associated inguinal hernia.

The slide technic was used, with heparinized rabbit plasma and embryonic tissue extract (chick) as mediums. One of the cultures of the descended canine testes had to be discarded because of contamination. The series were comprised of single and multiple plants of fragments varying widely in size. The growths were carried for periods of five to sixteen days, being fed every third day with the tissue extract and plasma mentioned. There was no lysis of the clot. The cultures were all sterile at the end of the experiments. Sections and whole plants were fixed at various intervals and stained with Heidenhain blue.

The results are given in table 2. In general, in both the human and canine series fibroblasts were seen early (within forty-eight hours). The cultures were on the whole predominantly fibroblastic, even though the amount of tissue extract was varied in some cultures. The rate of growth was slow, as would be expected in adult tissue. In many of the cultures round clear cells appeared at the periphery, which have not been definitely identified. No studies on the phagocytosis of dye were made. In some of the sections there were many polyblastic cells. The epithelial nature of the tissue was not apparent in any of the growths. In neither the descended nor the undescended testes series did characteristic or specific germinal cells develop (fig. 3).

In the explant of the rabbit testis great masses of cells were seen pushing their way out from the edge. In general, these masses were darkly granular at the center and were covered at the outer surface with from one to three layers of clear, round cells, varying between 18 and 28 microns in diameter. They were regularly arranged and suggested a vertical section through an epithelial membrane. In these cultures there were also free cells, some of which were ameboid, which were probably related to the clear, round cells mentioned.

It should be pointed out that there is an unusual tendency for normal testis, especially rabbit testis, to coagulate when fragmented. This may be overcome by extensive and rapid serial dilution.

In comparing the cultures of the descended and undescended testes of man and of the dog, there was no absolute sign of differentiation in

TABLE 2.—*Results of Tissue Culture of Testes*

Source	Patient	Age	History	Treatment	Histology	Duration of Culture	Results
1. Human undescended testis	1 (E. R.)	26 years	Left indirect inguinal hernia and inguinal retained testis	Orchiopexy plus biopsy plus culture; hernioplasty	Atrophic testis	19 days	Active fibroblastic growth; no specific cells; many free cells along edges—"amebocytes"
2. Human undescended testis	2 (I. M.)	34 years	Right indirect inguinal hernia plus undescended testis at extreme right	Orchidectomy plus culture; hernioplasty	Atrophic testis	13 days	Active fibroblastic growth; no specific cells; "amebocytes"
3. Human undescended testis	3 (M. L.)	0 years	Left inguinal retained testis plus inguinal hernia	Orchiopexy plus biopsy plus culture	Prepubertal	1 day	Good fibroblastic growth and some round, clear cells; "amebocytes," no differentiation
4.		21 years	Hydrocele, right	Orchidectomy	....	6 days	Cultures showed fibroblasts and a few "amebocytes"; a few rather irregular cells with 1 or 2 processes (fibroblasts in mitosis)
5. Human descended testis	....	....	Hydrocele	Orchidectomy	....	13 days	Fibroblastic cellular periphery; "amebocytes"; proliferating polyblasts
6. Human descended testis	... .	....	....	....	....	7 days	Fibroblastic
7. Human descended testis	... .	....	....	Orchidectomy	....	8 days	Fibroblastic, branched forms
8. Canine descended testis	... .	Adult	....	....	Normal	6 days	Slow growing fibroblasts
9. Canine descended testis	....	Adult	....	....	Normal	2 days	Contaminated
10. Canine undescended testis	... .	Adult	Abdominal retained right testis 2 by 1.5 by 1.5 cm.	Orchidectomy	....	5 days	Fibroblasts; peculiar stellate cells; polyblasts
11. Rabbit descended testis	....	Adult	....	....	....	6 days	Fibroblasts, "amebocytes"; stellate cells; epithelial strands
12. Rabbit descended testis	....	Adult	....	....	....		
13. Rabbit descended testis	....	Adult	....	....	....		

either series. It should be stated that 2 of the human retained gonads had an atrophic appearance histologically, while the other had the microscopic characteristics of a prepubertal gland. The growths for the most part were fibroblastic and nonspecific. Only in the rabbit series was the epithelial nature of the culture apparent. There was no marked
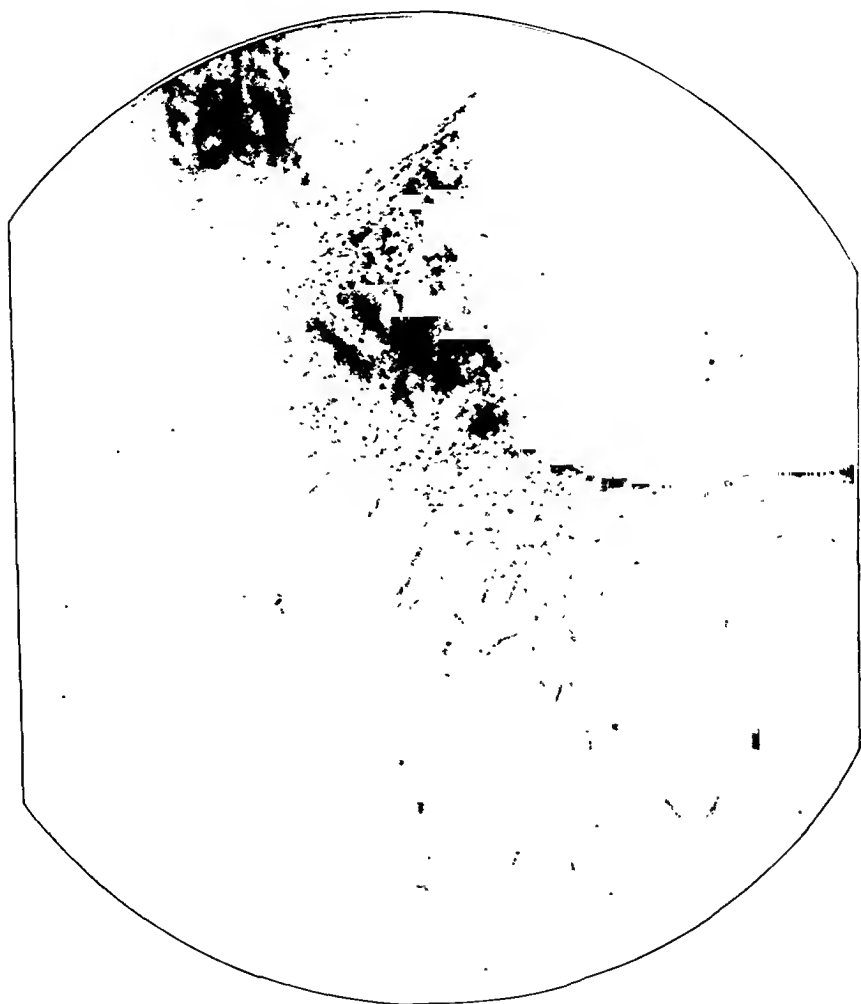
Fig. 3.—Tissue culture of an undescended human testis (case 1, table 2). Note the fibroblasts; at the periphery of the growth are darker round cells, one of which is in mitosis. No specific cell types are seen.

difference between cultures representing descended and undescended gonads. This may mean that undescended and descended testes have the same fundamental potentialities, but in view of the lack of positive differentiation one should not rationalize too far. All that can be said

at present is that there does not seem to be any difference in the line of development in tissue cultures representing descended and naturally cryptorchid, testes.

5. *Effect of Ligating Between the Testes and the Epididymis of the Dog.*—In this clinic studies have been made of the undescended testis to note any abnormality in the pathways for seminal transmission. If such a defect exists, its relation to the degenerative changes in the ectopic testis is of speculative interest. While it is established that the imperfection of the cryptorchid testis is due partly at least to the thermal and pressure effects resulting from its abnormal position, it has never been denied that some undescended testes are anatomically malformed ab initio (Wangensteen). A common finding in the undescended testis is the separation of the epididymis from the testis. How often this occurs normally is unknown. As mentioned before, the undescended testis is often smaller than its scrotal fellow.

My interest in this subject was increased by the inability on 6 occasions to find a supposedly retained testis at operation.

CASE 1.—L. H., a boy aged 8 years, was admitted to the University Hospitals on June 4, 1930 and discharged June 17.

On admission the diagnosis was bilateral undescended testis, present since birth.

On physical examination the left testicle could not be palpated, but the right testicle could be felt in the inguinal canal. It was freely movable but could not be brought into the scrotum.

When the patient was operated on, the gubernaculum was seen to come down posterior to the parietal peritoneum and to embed itself deep to the Poupart ligament. There was no definite evidence of testis. Exploration of the retroperitoneal space and peritoneal cavity with the finger revealed no testis. A small hernial sac was felt.

Microscopic sections of the tissues removed showed several lymph nodes, gubernaculum and vas deferens. A hernioplasty was performed on both sides and an orchiopexy on the right.

CASE 2.—W. O., aged 16 years, was admitted to the University Hospitals Oct. 15, 1935, and was discharged November 11. Since birth he had had undescended testes. He had never noticed the testes in the scrotum or felt them in the canals. The family physician had made an injection into the left inguinal canal for hernia.

Physical examination revealed the penis and scrotum to be somewhat underdeveloped. The testicles were not felt in the scrotum or in the inguinal region. The patient had a congenital cardiac lesion, probably on the basis of pulmonary stenosis. His general appearance was that of a cretin.

A prostatic smear produced no spermatoza. The basal metabolic rate was + 6 per cent.

On October 18, exploration was done through a right oblique inguinal incision. No testis was found. Dissection was made into the retroperitoneal region as far as the bifurcation of the aorta. The peritoneal cavity was opened also, but no trace of testis, vas deferens or gubernaculum was found. A hernioplasty was performed, and the wound was closed. On November 11 an orchiopexy was performed on the left side.

CASE 3.—A. B., aged 24 years, was admitted to the hospital June 13, 1935, and discharged June 25. The patient said that the left testicle had never been felt. The right testicle had always been normal in size and position. No hernia could be demonstrated on physical examination, nor could the left testicle be palpated.

On June 14, through a left inguinal incision, the region was explored. There was a spermatic cord, in which the vas deferens and vessels were found. No testis was found. The retroperitoneal space was explored. No testicular tissue being found, the vas deferens was amputated near the bladder and the spermatic cord cut high in the retroperitoneal region. A small hernial sac was found, which was ligated. A Bassini hernioplasty was done in the usual fashion.

CASE 4.—R. U., aged 11 years, was admitted to the hospital July 24, 1935, and discharged August 7. The patient had a right inguinal hernia and bilateral undescended testis. One year previously a herniorraphy had been performed on the right side in another hospital, at which time no right testis was found.

On July 25 the patient was operated on, and a recurrent right inguinal hernia was repaired. A normal spermatic cord was found, but no definite testis was isolated. In the retroperitoneal space there was a small piece of tissue that was thought to be testis, as there was a small vascular pedicle running from it toward the renal region. This tissue and the spermatic cord in the inguinal region were removed for histologic study. A hernioplasty was performed according to Andrews' technic.

Microscopic sections of the removed tissue showed fibrous tissue, blood vessels and a small lymph node.

CASE 5.—W. R., aged 20, was admitted to the hospital March 16, 1938, and was discharged March 28.

The patient had had undescended testes since birth. A year previously the family physician had tried gonadotropic substance (antuitrin-S), with no results.

The right testis could be felt overlying the external oblique aponeurosis, having migrated out to the external abdominal ring. There was an indirect inguinal hernia. A testis could not be felt, nor was there a hernia on the left side.

A right orchiopexy and hernioplasty had been performed on Dec. 3, 1937.

The patient returned March 16, 1938, at which time the scrotal-crural anastomosis on the right was undone and exploration was carried out through a left oblique inguinal incision. The conjoined tendon was intimately attached to the external oblique aponeurosis at Poupart's ligament. There apparently was no vas deferens. A tiny remnant of a structure deriving from the bladder on the outside of the peritoneum may have represented the vas deferens. The gubernaculum extended into the scrotum. No testis or spermatic vessels could be found.

A hernioplasty was performed.

Microscopic sections of the tissues removed revealed probable vas deferens, fibrous tissue and blood vessels; there was no testis.

CASE 6.—G. S., aged 8 years, was admitted to the hospital Aug. 12, 1930, and discharged August 23. For two years prior to his admission it had been noted that the left testis of the patient was not in the scrotum. At no time had the condition caused him any discomfort.

Physical examination gave essentially negative results except that no left testicle could be felt. The right testis was normal in size, shape and position. The external genitalia were normal.

On August 13 an operation was performed. When the external oblique aponeurosis was divided the terminal end of the spermatic cord was seen to insert

into the outer leaf of the external oblique aponeurosis. It did not extend into the scrotum. With the slightest traction it was detached. When this was followed medially the vas and spermatic vessels were seen, both of which were extremely small. What seemed to be testis and epididymis were mere nubbins of tissue, about one-fifth or one-sixth the size of the other testis. This tissue was removed, but on cut section it proved to be scar tissue. No testis was found. An indirect inguinal hernia was repaired.

Microscopic study of the removed tissue showed no evidence of testicular tissue. Epididymis, spermatic cord, spermatic blood vessels, muscle and fibrous connective tissue (gubernaculum?) were present.

These 6 cases are examples of probable monorchism, and the incidence of 6 in a series of 143 cases of cryptorchidism seen at this clinic to date is of questionable significance. Theoretically, if one considers the undescended testis to be congenitally imperfect, one would expect to find a gradation from anorchism to almost perfection. However, most of my cases would belong to the group showing the upper stages of development. Moreover, up to puberty it is impossible to differentiate grossly or microscopically between the descended and the retained testis. Knowing the effects of an extrascrotal environment on the testis, it seems safe to say that the retained testis is not necessarily congenitally imperfect, but that it may become degenerate as a result of its abnormal position.

The possibility that the degenerative changes in the ectopic testis may be due to some defect in the pathway of seminal transmission has been suggested. In the available literature, however, there is no report of any obstruction or lack of continuity in cases in which the testis, epididymis and the cord have been present. In this laboratory, attempts to force mercury and colloidal dyes through the duct system of the epididymis from the vas deferens have been unsuccessful in both normal and undescended testes. This is probably due to the secretion in the lumens, the size of the ducts and the winding arrangement of the tubules.

The work of Moore and other investigators seems to prove that occlusion of the ductus deferens leads neither to testicular degeneration nor to interstitial hypertrophy. Van Wagenen, Oslund, Cunningham and Knaus concluded that closure of the ducts issuing from the testis (vasa efferentia) leads to destruction of the germinal epithelium. Moore, however, questioned this, since testicular grafts recovered six months after transplantation of immature testes show spermatozoa. He believed that he had conclusive evidence against this view, since he had examined a guinea pig with congenital absence of the wolffian duct. The testes of this animal were normal in size and appearance and occupied a scrotal position. One testis lacked vasa efferentia, the epididymis and a portion of the vas deferens, which did not reach the urethra. No seminal vesicles were present. The testis which had never had vasa efferentia or the epididymis showed approximately 50 per cent of the

seminiferous tubules in a normal state, with quantities of spermatozoa. Moore stated that since production of germ cells continues even in the absence of vasa efferentia, occlusion of these ducts cannot be held responsible for testicular degeneration. Moore's work has been criticized, however, in that the evidence which he presents is inferential and not direct.

Most of the aforementioned experiments were performed on rats, cats, mice, rabbits and guinea pigs. The following experiments were performed to study the effect of ligating between the epididymis and the testis of the dog.

Twenty-one animals were studied. Healthy adult dogs, weighing from 11 to 25 Kg., were anesthetized with pentobarbital sodium. In 12 cases, the testis on one side was exposed, and under aseptic precautions a silk ligature was placed where the epididymis and the testis joined. In the other 9 cases this juncture was cut across between silk ties. The opposite testis was also exposed and manipulated at the same time, as a control. After material for biopsies had been taken, the testes were placed in the scrotum. At periods of from two days to eleven months the testes were removed and studied. It should be stated that attempts were made not to compromise the blood supply of either the testis or the epididymis, but some vessels unavoidably were included in the ligatures. After the ligation the testes in every instance were firm, tense and congested in color. Fifteen of the organs were removed after periods of from seven to eleven months. The testis on which operation had been done in these 15 cases was always smaller and more atrophic than that on the control side, and its capsule was much thicker. However, on microscopic examination, except for fibrosis and tubular atrophy near the periphery of the testis, which was probably an effect of pressure, there was no noticeable tubular degeneration or increase in interstitial tissue as compared with the control testis and other normal testes. No relative or absolute histologic differences could be ascertained between the two series except that in the cases in which operation was done the cells lining the tubules were larger and darker-staining than those of the control testis. There were numbers of spermatozoa in the lumens of some of the tubules of the testes with obstruction (table 3).

These experiments would tend to confirm Moore's statement that occlusion of the efferent ducts of the testis does not result in testicular degeneration. Evidently spermatogenesis can exist even with no efferent pathways of the testis. The significance of this finding in attempts to explain the degenerative changes in the ectopic testis as a result of some defect in the pathway of seminal transmission, even if present. is at once apparent.

6. *Quantitative Study of the Interstitial Cells of the Undescended Testis.*—In the literature it is said that a compensating hypertrophy of the interstitial tissue occurs in the cryptorchid testis (Bouin and Ancel), but whether this increase is relative or absolute has never been accurately determined. Bascom in a critical review gave a method for determining the relative amounts of interstitial and tubular tissue in

TABLE 3.—*Effect of Tying Between Epididymis and Testis in Dog*

Dog No.	Weight, Kg.	Side on Which Operation Was Done	Duration of Ligation	Results—Treated Testis		Results—Control Testis	
				Gross	Microscope	Gross	Microscope
1	21.0	Left (ligation)	2 days (dog died)	....	Some disorganization and giant cells in tubules; tubules not as cellular	....	Fairly normal
2	13.7	Left (ligation)	1/8/35 3/14/35	⅔ size of right testis; tunica adherent; skin and subcutaneous tissue ¾ inch (2 cm.) thick	Tubules full; dark-staining round cells; tubules smaller; some tubules normal; sperm present	Capsule slightly thickened	Some disorganization in tubules
3	14.0	Left (ligation)	1/9/35 10/5/35	Testicle embedded in scar tissue; blood supply normal	Atrophy toward periphery; centrally normal	....	Normal
4	12.3	Left (ligation)	1/9/35 12/4/35	Very atrophic	2 mo. later biopsy showed atrophy and separation tubules; at 11 mo., still some atrophy but picture improved	....	At 2 mo., atrophy and disorganization; at 11 mo.. practically normal
5	22.0	Right (ligation)	1/11/35 3/12/35	Skin, subcutaneous tissue and tunica 0.75 cm. thick; testis atrophic and fibrotic	Marked atrophy	....	Normal; approximately same as biopsy at operation
6	25.0	Left (ligation)	1/11/35 11/6/35	Slightly smaller than right	2 mo., slightly disorganized but fairly normal; 10 mo., normal	....	2 mo., gland disorganized, but fairly normal; 10 mo., normal
7	12.0	Left (ligation)	1/21/35 11/13/35	....	2 mo., slightly disorganized and atrophied; 10 mo., fairly normal	....	10 mo., normal
8	11.0	Right (ligation)	1/26/35 12/5/35	....	Atrophy at periphery; normal in center	....	....
9	12.0	Left (ligation)	1/29/35 2/1/35	Dog died of peritonitis; cholecystectomy	Disorganized	....	Disorganized
10	25.0	Left (ligation)	2/8/35 11/7/35	Epididymis was separated from testis at operation	Atrophy at periphery; centrally normal	....	Normal
11	18.0	Left (ligation)	2/12/35 2/14/35 (distemper)	....	Disorganization	....	....
12	15.0	Left (ligation)	2/23/35 11/7/35	....	Fairly normal	....	Normal
13	12.5	Left (division)	3/13/35 11/13/35	....	Tubules have larger and darker staining cells; atrophy toward periphery; otherwise fairly normal	....	Atrophy toward periphery, normal centrally.
14	16.4	Left (division)	3/26/35 10/5/35	....	Normal; numerous spermatozon	....	Normal
15	...	Left (division)	3/26/35 10/30/35	....	Normal; deeper stained	....	Normal
16	...	Left (division)	3/26/35 12/5/35	....	Normal cells in lumens of tubules larger and darker stained	....	Normal
17	...	Left (division)	3/26/35 10/30/35	....	Normal	....	Normal
18	...	Left (division middle)	4/2/35 11/12/35	....	Normal	....	Normal
19	15.0	Left (division middle)	4/2/35 11/12/35	....	Normal	....	Normal
20	12.3	Left (division)	....	....	Normal	....	Normal
21	11.0	Left (division lower ½)	4/2/35 1/2/36	....	Normal	....	Normal

the testes and denied that a compensatory hypertrophy of the interstitium occurs in the testis of the naturally cryptorchid pig. He based his conclusions on studies of unilaterally cryptorchid animals in which the other testis was absent, presumably as a result of castration. For this reason his work was not adequately controlled.

In this study, full grown dogs (except dog 5, which was young) were rendered cryptorchid, and the amounts of interstitial and tubular tissue were determined to see if there was a relative or an absolute change in the amount of interstitial tissue. With the animal under pentobarbital sodium anesthesia, the right testis was exposed, and after material for biopsy had been taken the gonad was placed in the inguinal region or in the abdomen. After three months, both the right testis and the left (control) testis were removed. Histologic sections were made and stained with hematoxylin and eosin. A drawing of a representative field from a section of each testis was made with a projection apparatus. Tracings of these sketches were cut out with scissors, and the tubular and interstitial areas were weighed separately. From these weights the relative percentages of the two tissues were estimated. The weight of the testis being known, the weights of the interstitial tissues and the tubules could be calculated. The results of the calculations are given in table 4.

Of 11 dogs in which cryptorchidism was experimentally produced 7 showed an increased percentage of interstitial tissues in the "undescended testis" after three months of abdominal or inguinal retention as compared with the control gonad, 3 exhibited a decrease, and 1 (dog 11) showed practically no change. In all cryptorchids except dog 3 there was a decrease in the actual weight of the interstitial tissue of the abdominal or inguinal testis. This would tend to show that in experimentally produced cryptorchidism the increase in interstitial tissue is relative and not absolute, the relative increase being due to the tubular degeneration and the absolute decrease being due to the generally smaller size and weight of the gonad. Whether these deductions hold true for the testis of the naturally cryptorchid dog is unknown. Bascom and Moore pointed out that there are variations in the amount of interstitial tissue in different species. Also, Moore called attention to the danger of speculating as to the degree of function from the amount of interstitial tissue.

7. *Effect of Serum from Pregnant Mares on the Testis of the Cryptorchid Dog.*—Wells reported the effect of serum from pregnant mares on the reproductive organs of a hermaphrodite ground squirrel. Subcutaneous injection of the serum in a dose of 25 rat units twice daily for eighteen days caused precocious production of spermatozoa in the right ovotestis, which descended to the scrotum, and also induced the formation of graafian follicles and corpora lutea in both ovotestes. All the male accessory reproductive organs of the hermaphrodite showed great stimulation, probably owing to the stimulation (by gonadotropic substance) of the animal's own ovotestes to release male hormone. In

TABLE 4.—*Relative Amounts of Tubular and Interstitial Tissue in Undescended Canine Testis*

Dog	Weight, Kg.	Right Testis							Left Testis							Position of Right Testis
		Weight, Gm.	Size of Testis, Cm.	Tubular Tissue %	Tubular Tissue Gm.	Interstitial Tissue %	Interstitial Tissue Gm.		Weight, Gm.	Size of Testis, Cm.	Tubular Tissue %	Tubular Tissue Gm.	Interstitial Tissue %	Interstitial Tissue Gm.	
1	16.8	12.55	4×2.5×2	77.0	9.66	23.0	2.89		13.33	4.5×3×2.5	71.0	9.80	26.0	3.15	Inguinal
2	16.8	10.0	3.5×2.5×1.5	74.6	7.46	25.4	2.54		17.2	4.5×3×2.5	73.1	12.56	26.9	4.64	Inguinal
3	18.1	10.0	3.25×2.5×1.5	63.0	6.3	37.0	3.7		12.6	4×2.5×1.5	71.6	9.01	28.4	3.59	Inguinal
4	13.6	5.7	3×2×1.5	64.7	3.68	26.3	2.02		13.55	4×2.75×2.5	70.6	9.56	29.1	3.99	Inguinal
5	8.2	2.5	1.8×1×1	53.1	1.32	46.0	1.28		3.5	3×1.5×1	58.7	2.03	41.3	1.45	Inguinal
6	9.1	7.7	3×2×1.5	64.5	4.96	35.5	2.74		13.7	3.5×2.75×2	67.5	9.25	32.5	4.45	Inguinal .
7	6.4	7.0	2.5×2×1.5	74.3	5.2	25.7	1.8		10.0	5×2.5×2	71.4	7.14	28.6	2.86	Abdominal
8	6.8	6.6	2.75×2×1.5	66.6	4.4	33.3	2.2		11.3	3.5×2.5×2	70.0	7.91	20.0	3.39	Abdominal
9	16.3	5.2	2.5×1.5×1.5	69.7	3.63	30.3	1.57		10.5	3.5×2.5×2	72.5	7.61	27.5	2.89	Abdominal
10	21.8	14.1	2×1.5×1	56.8	8.01	43.27	6.09		20.0	4×3.5×3	67.3	13.1	32.7	6.3	Abdominal
11	25.4	16.2	3.5×2×1.5	71.4	11.41	29.6	4.79		20.0	4×3.5×3	71.0	14.2	29.0	5.8	Abdominal

another hermaphrodite ground squirrel, which was untreated and which served as a control, the seminiferous tubules lacked lumens but possessed many spermatogonia and occasionally primary spermatocytes. While one does not know whether the treated ovotestis contained spermatozoa before the injection, the presumptive evidence is strong that injection of serum from pregnant mares caused the production of spermatozoa in the ground squirrel (Wells, Wells and Moore). Moore found that mare serum failed to induce formation of spermatozoa in young rats, but Cole, Guilbert and Goss found that the number of spermatocytes was increased in the testes of young rats so treated.

In this study, the right testis of each of 3 adult dogs was elevated to the abdomen, and after the gonad had been there for three months injections of pregnant mare serum were instituted to note any effects on the testis. One hundred and fifty rat units was injected subcutaneously into the flank every other day for a period of seventeen days (1,350 units). The pregnant mare serum was obtained from an eight months pregnant mare at the University Farm School, St. Paul, Minn. The serum was kept sterile and standardized, spayed virgin rats about 160 Gm. in weight being used, so that 1 cc. of the injected serum was equivalent to 150 rat units. On the eighteenth day, the right testis and the left (control) testis were removed. The right testis in every case was embedded in scar tissue and had not descended into the scrotum. It was smaller in size and weight than the scrotal testis.

Right Testis

Dog	Weight, Kg.	Size, Cm.	Weight, Gm.
1	28	3½x2 x1⅓	16.2
2	24	2 x1½x1	14.1
3	18	2½x1½x1½	5.2

Left Testis

Dog	Weight, Kg.	Size, Cm.	Weight, Gm.
1	..	4½x3 x2½	18.3
2	..	4 x3½x3	20.0
3	..	3½x2½x2	10.5

When the testes had been measured and weighed, sections were made and stained with hematoxylin and eosin. The microscopic appearance of the cryptorchid testis was interesting (fig. 4). It was surprising how closely it approached the structure of the normal gland. Tubular degeneration was slight. The interstitial tissue showed little if any increase, and germinal epithelium with spermatozoa was present in all 3 cases. Unfortunately, material for biopsy was not obtained before the injection therapy was begun, but spermatozoa were never seen histologically in testes which had been elevated to the abdomen for three months.

A similar study was carried out with 6 other dogs, weighing from 15 to 22 Kg. The right testis was elevated to the abdomen, and after a two week period of healing 150 rat units of the same pregnant mare serum was injected subcutaneously into the flank weekly for a period of six months. At the end of that time the dog was castrated, and the abdominal and the scrotal testis were examined. Histologically, the abdominal glands of 3 dogs showed fairly normal germinal epithelium; in 1 there were areas of degeneration, and in the other 2 there was

definite degeneration. In my experience, when the testis of an adult dog has been elevated to the abdomen for six months, it always shows degenerative changes (control).

The results of these studies are important, for here is a substance that will maintain the germinal epithelium in spite of an aberrant posi-
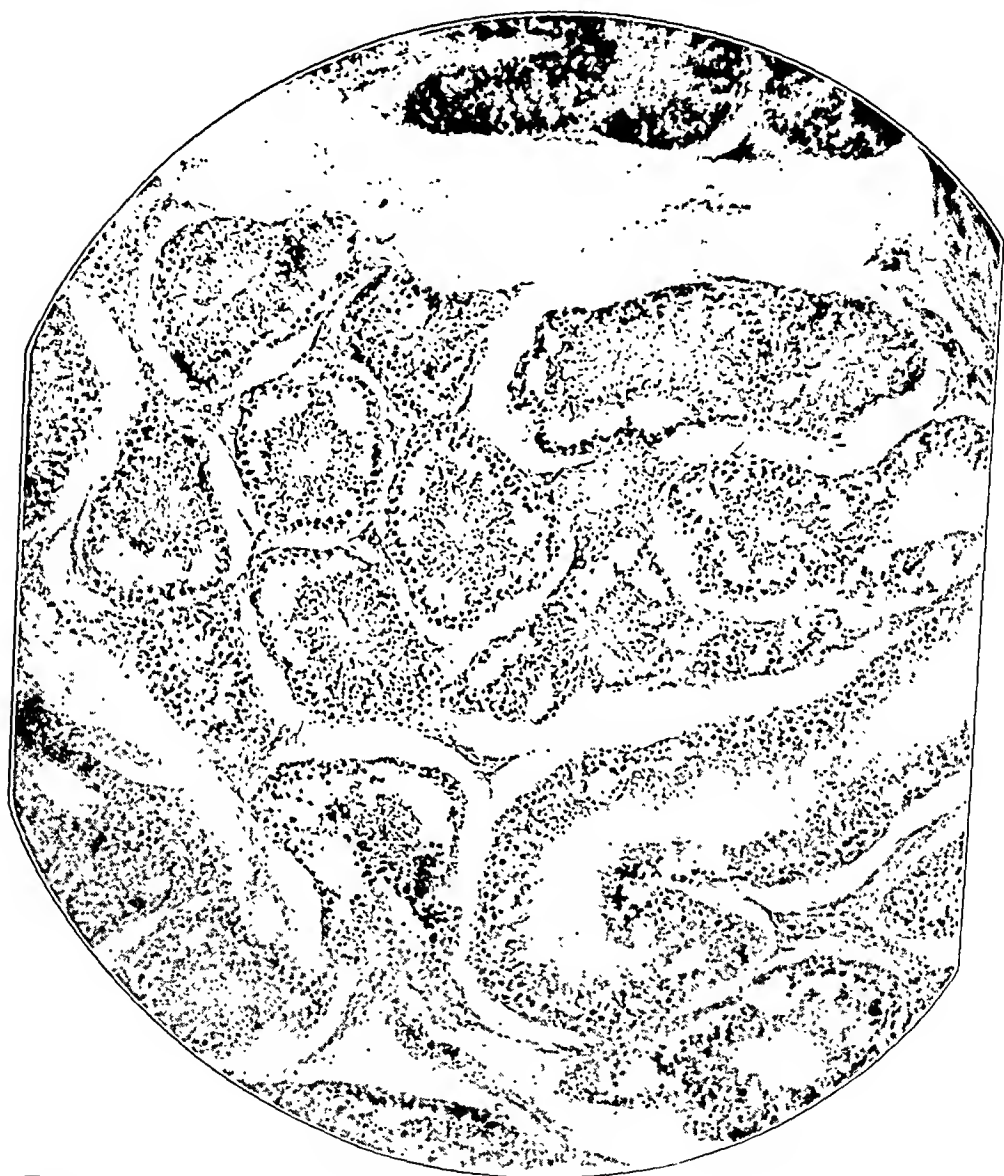
Fig. 4.—Section of an experimentally produced undescended testis of a dog treated with serum from a pregnant mare. Note that the tubules have mature germinal epithelium; spermatozoa are present in most of the tubules. The degree of maturity closely approaches that of a normal descended testis.

tion of the gonad. The question arises as to which is more important: the scrotal (thermoregulatory) or the gonadotropic influences in maintaining the normal testicular function. The importance of the thermoregulatory mechanism of the scrotum in relation to spermatogenesis is

well known from the work of Moore and Wangensteen. The reason why most mammalian testes are susceptible to degeneration caused by their own body heat is unknown. In birds, with a higher body temperature than mammals and with abdominal testes, this thermoregulatory mechanism does not hold. Similarly, in some mammals, such as the whale, elephant and rhinoceros, which do not have scrotums, spermatogenesis is compatible with an intra-abdominal position of the gonad. Moore has suggested that in the latter there may be a correlation between the absence of a scrotum and a lower or less constant body temperature. It may be also that in animals with functional intra-abdominal testes the pituitary gland is more active, regulating the spermatogenic mechanism without benefit of a scrotum. At least the work of Wells and this study would suggest that in certain animals gonadotropic substances may keep the histologic character of the testis normal without the thermoregulatory influence of the scrotum. This might be a partial explanation of the instances of fertility in patients with bilateral cryptorchidism. The final answer, however, awaits further investigation.

8. *Effect of Bringing the Naturally Undescended Testis into the Scrotum.*—It is important to know whether undescended testes when brought into the scrotum will develop normally. In fact, the chief reason for doing an orchiopexy is the hope that maturity will ensue as a result of scrotal position. Most surgeons have been more interested in the cosmetic than in the functional result of operations on the retained gonad. The following results have been noted when the naturally undescended testis has been brought into the scrotum, in man and in animals:

(*a*) Dog. In 1933-1934, 4 adult cryptorchid dogs, weighing 7.5 to 11.15 Kg., were observed in the experimental laboratory. One of these dogs may have been an incomplete castrate; the others had left inguinal testes. With the dogs under pentobarbital sodium anesthesia, both the descended and the undescended testis of each animal were exposed and measured, aseptic precautions being used. After material for biopsy had been taken the undescended testis was anchored in the scrotum. The descended or control gonad was replaced in the scrotum. Three months later the dogs were castrated, and the testes were again measured. In every instance the undescended testis, which had been placed in the scrotum, was smaller than before operation. Microscopic sections of all gonads were made and stained with hematoxylin and eosin. Histologically there was little difference between the biopsy material taken before and that taken after orchiopexy. The previously ectopic organ still had an atrophic appearance. No spermatogenesis was seen. The microscopic sections of two of the descended testes were normal except for some evidence of disorganization even after three months. This emphasizes that great care must be exercised in handling the testis at operation (table 5).

TABLE 5.—*Effect of Scrotal Fixation on the Naturally Undescended Testes of Adult Dogs*

Dog	Weight, Kg.	Age	Descended Testis				Undescended Testis			
			Gross, Before	Microscopic, Before	Gross, After	Microscopic, After	Gross, Before	Microscopic, Before	Gross, After	Microscopic, After
1	7.5	Adult	....	Normal	Thickened capsule; 1.5×0.5×0.5 cm.	Some degeneration, occasional sperm in tubules	1×0.25×0.25 cm. (left inguinal)	Atrophic; no sperm; outline tubules; 1-2 cells on basement membrane	1×0.25×0.25 cm., thickened capsule	Same; more debris in lumens of tubules
2	11.5	Adult	2.5×2×2 cm.	......	....	Tubules full of large dark cells; sperm present; slight disorganization	2.5×2×1.5 cm. (left inguinal)	Very atrophic no sperm; interstitial hypertrophy very prominent	2×1.5×1.5 cm.; thickened capsule fibrous	Same as before
3	10.0	Adult, over 2 yr.	3.5×2×2 cm.	Slight disorganization; sperm present	3.5×2×2 cm.; capsules slightly thickened	Same as before	Left inguinal	....	2×1.5×1 cm.	Very atrophic hyalinized interstitial tissue; no sperm
4	9.5	Adult	....	....	3×2×1.5 cm. capsules slightly thickened	Tubules full of large dark cells; sperm present; very little interstitial tissue	Right inguinal; vas deferens ended in nubbin of tissue about 1.5×1 cm.	Very atrophic; tubular structure (epididymis?); much connective tissue; no definite testicular tissue	Small fibrous mass	Lymphocyte infiltration; indefinite tubular structure; incomplete castrate?

Two factors may have influenced these results: 1. The dogs were full grown and the germinal epithelium may have been too atrophic to regenerate. 2. In none of the dogs did the surgically treated testis remain low in the scrotum; instead, it attained a high position near the base of the penis.

(*b*) Pig. While the results of operation on dogs were disappointing, better results have been obtained from performing orchiopexy on pigs.

Wangensteen reported the results of orchiopexy in 3 young pigs with congenital inguinal testes which had the microscopic appearance of prepubertal gonads. Two, four and ten months after operation respectively, the animals were killed and biopsies of the surgically treated testes revealed mature germinal epithelium with spermatozoa. In other pigs, in which the abdominal testis was anchored beneath the skin of the groin, mature germinal epithelium was not observed. Since spermatogenesis has never been observed in sections of the undescended testis of the adult boar in this laboratory, it cannot be denied that the germinal epithelium is improved by fixation of the testes in the scrotum.

These results are the same as those previously observed by Moore, Wangensteen and others when in the dog and guinea pig the testis previously placed in the abdomen has been replaced in the scrotum and seen to regenerate. However, experiments with naturally cryptorchid pigs give more conclusive proof of the value of orchiopexy, because the results are free from objections which might be raised against the use of the animals in which cryptorchidism had been produced experimentally.

In comparing the results obtained from orchiopexy in natural cryptorchids with those of the same operation in the experimental variety, it is to be noted that the degree of maturity obtained in the former is never as great as that occurring in the latter (Wangensteen).

(*c*) Man. At the University Hospitals for the past few years, smears and biopsies have been made of material from undescended testes at the time of orchiopexy. The ages of the patients varied from 9 to 26 years. Microscopic sections from 17 and smears from 8 of these did not disclose spermatozoa. When the scrotum was detached from the thigh, usually six months after the orchiopexy, a small amount of material for biopsy was again taken from the periphery of the testis. Histologic study of the material from 4 of these patients (15 to 24 years of age) showed no spermatozoa. The germinal epithelium, while occasionally improved, never showed complete maturation. However, a case reported by Wangensteen is of particular importance:

The patient was first seen at the age of 20 years. He had inguinal testes, for which he was treated by orchiopexy, first on the right and then on the left.

Biopsy at operation showed tubules with atrophic epithelium and no spermatozoa. Sections of the testes removed at the time of detachment of the scrotum from the thigh four and six months later revealed an improved but not mature germinal epithelium. No spermatozoa were seen. Sixteen months after the latter operation the patient was accidentally killed.

At postmortem examination the testes were low in the scrotum and were about two thirds the normal size. The histologic appearance of the right testis was nearly normal. The left testis, while exhibiting some normal spermatogenesis, showed more atrophy than maturation. Examination of the semen one week before death had revealed only occasional spermatozoa. This is the only clinical case recorded in available literature which definitely proves that the germinal epithelium of the human undescended testis may improve after orchiopexy.

Possibly in most of my cases histologic examination was made too early to permit determination of the degree of maturity which might finally be attained. Access to the whole gland, as in the case of the castrated animal, for multiple smears and sections might alter the results obtained when smears and sections of the undescended testes are studied for signs of maturation. Moreover, the histologic effect of orchiopexy in Wangensteen's case and the undoubted examples of fertility in human cryptorchids cast further doubt on these negative results. Finally, since potential fertility may persist into adult life in lower animals with undescended testes, the sum of the evidence tends to indicate that nearly all patients with undescended testes should be subjected to orchiopexy.

9. *Effect on the Naturally Undescended Testis of the Use of Various Preparations of Gonadotropic Substance from the Urine of Pregnant Women and from the Anterior Lobe of the Pituitary.*—(a) Dog. Antuitrin-S [3] was injected into 2 adult dogs, weighing 10 and 12.5 Kg., respectively, with congenital unilateral inguinal testis. One hundred rat units (1 cc.) was injected daily subcutaneously until 3,000 units had been given. Descent was not observed in either case. One month later the testes were removed.

Each undescended testis was embedded in fibrous connective tissue and was smaller than its normally located fellow. Microscopic section failed to reveal any spermatozoa, and the organs had the usual atrophic appearance. Smears of the cut surfaces failed to show spermatozoa. Studies of the relative amount of interstitial tissue and of the size of the tubules could not be made before and after treatment, since removal of material for biopsy before treatment would have altered the appearance of the testes. Unfortunately, the pituitary glands of these animals were not studied (fig. 5).

The doses of antuitrin-S were the same as those used for man. Considering the difference in body weight, this was an excessive dose.

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3. Antuitrin-S (Parke, Davis & Co.) is a gonadotropic substance extracted from urine of pregnant women.

This may have influenced the results, but the age of the dogs and the fibrous adhesions surrounding the testes were probably the more important factors.

(*b*) Man. For the past four years, at the University Hospitals, undescended testes in some cases have been treated by the administration of
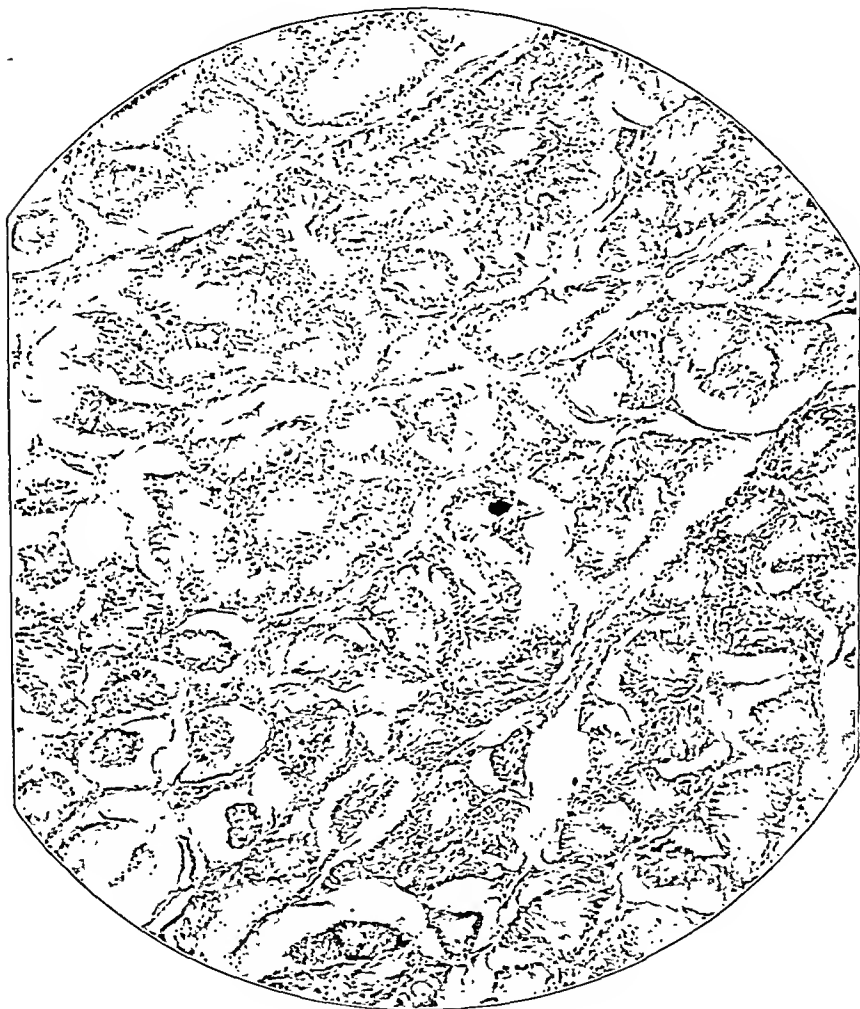
Fig. 5.—Congenitally undescended testis (× 700) of an adult dog treated with antuitrin-S (3,000 units). The usual degenerated appearance still persists. Compare with figure 1.

gonadotropic substances. Schapiro in 1930 reported having obtained genital growth and testicular descent in boys and young men with hypogenitalism and cryptorchidism by the use of the gonadotropic substance from the urine of pregnant women. Since then the literature has con-

tained reports of several series of cases in which undescended testis was treated by the use of this material. Thompson and his associates and also Cramer have recently summarized the results of most of the investigators; in over 70 per cent of cases descent of the retained gonad has occurred. How critically some of the cases were observed may be questioned when in one series the testis was reported to have descended within three hours after treatment (Harris). About half of the patients showed signs of hypopituitarism or adiposogenitodystrophy and received other therapy besides that employing gonadotropic substances (e. g., treatment with thyroid extract or a dietary regimen). From a summary of published data, the original position of the gonad successfully brought into the scrotum by the gonadotropic substance obtained from the urine of pregnant women was as follows: high scrotal, intra-abdominal and inguinal, in the order named (Thompson and others).

Kunstadter and Robins, Schapiro, and Goldman and Stern concluded that the administration of the gonadotropic substance obtained from the urine of pregnant women is indicated in hypopituitarism of the male characterized by genital underdevelopment. However, the clinical diagnosis of pituitary or other endocrine dyscrasia is always subject to considerable variation in interpretation. Hess, Kunstadter and Saphir expressed the opinion that if cryptorchidism could be studied with more objective criteria a more rational therapy could be instituted. It is known that whenever gonadal function is diminished or absent, as in adult hypogonadism, castration or the menopause (Evans, Engle and Smith), there is excessive excretion of gonadotropic substance, presumably of pituitary origin. Katzman and Doisy showed that the urine of normal children contains little or no gonadotropic substance. Hess and his co-workers reasoned that since in castrated persons or in cryptorchid boys the gonadotrpoic hormone is presumably of pituitary origin, it seems logical to conclude that the presence of gonadotropic substance in the urine of cryptorchids indicates that the anterior lobe of the pituitary gland is active in gonadotropic function. The appearance of the gonadotropic substance in the urine may be due to insufficient activity of the gonad, which failed to modify the hormone or to remove it from the blood. On the other hand, the occurrence of cryptorchidism with absence of gonadotropic substance from the urine may be interpreted to mean either that there is primary pituitary dysfunction or that the undescended testes are functionally active or that at least one of them is.

Accordingly, Hess and his associates determined in a semiquantitative manner the excretion of gonadotropic substance in the urine of cryptorchid boys before and after treatment with the gonadotropic substance obtained from the urine of pregnant women. Nine of their 13 patients with cryptorchidism responded to the use of the gonadotropic substance by descent of the testis and disappearance of gonadotropic

substance from the urine. They concluded that in the absence of mechanical obstruction to descent the best results from the use of this gonadotropic substance are obtained in those cases of undescended testis in which gonadotropic substance is present in the urine but disappears after treatment.

Hardy, Bigler and Scott reported results in one of the largest series of cryptorchids treated with gonadotropic substances that have been recorded to date. In one group, 32 boys with 40 undescended testes were treated with an extract of the anterior lobe of the pituitary gland which contained the gonadotropic principle. In 26 cases the testicles remained unchanged in location, in 4 there was partial descent, and in 10, or 25 per cent, there was complete descent. After treatment was discontinued, however, only 7, or 18 per cent, of the testes remained descended. In another group, gonadotropic substance from the urine of pregnant women (antuitrin-S) was used in the treatment of 23 patients with 31 undescended testicles. No change was observed in the location of 12 testicles; 4 descended partially, and 15, or 48 per cent, descended completely. However, only 14 testes, or 45 per cent, remained descended. Both extracts were used in the treatment of 16 boys with 20 undescended testicles. In 9 cases there was no change, in 2 descent occurred, and in 9, or 45 per cent, there was complete descent, which was permanent in 5, or 25 per cent. They found that descent of the testicle usually begins to take place before 4,000 rat units of gonadotropic substance has been given.

Undoubtedly, in the literature more prominence has been given to successes than to failures. Few contraindications to therapeutic use of gonadotropic substances are recognized, and the therapy is too recent to permit investigation of the possibility of late complications. Thompson and others obtained descent of 4 inguinally retained testes in 21 instances of cryptorchidism (19 per cent). Mimpriss, who obtained descent in only 6 of 20 patients with undescended testis who were so treated, concluded that the gonadotropic substance from the urine of pregnant women should be used chiefly for patients with bilateral cryptorchidism and subnormal genital development. Cabot referred to the possibility of late atrophy of the testes, and Cole produced atrophy of the tubules of the testes by high doses. Goldman and Stern commented on the possible development of precocious sexual maturity and for this reason gave 9 years as the earliest age at which treatment with gonadotropic substances should be started. In this clinic also there is some hesitancy in using the gonadotropic substance from the urine of pregnant women for very young children, but Dorff and also Aberle and Jenkins reported using it for children about 3 years of age with no untoward results. Geschickter and his associates found that young male monkeys given the gonadotropic substance from the urine of pregnant

women presented hypertrophy of the prostate and enlargement of the breasts. However, from a survey of the available literature and the experience at this clinic, the danger of most such complications would seem more theoretic than actual.

The results from the use of gonadotropic substances in the treatment of retained testes observed at the University Hospitals will be summarized now. Four products have been tried: antuitrin-S (Parke Davis & Co.), follutein (Squibb), prephysin (Chappel) and A. P. L. (Ayerst).[4] The last three products have been used in only a few cases.

Antuitrin-S. It has been my practice to inject 1 cc. (100 rat units) of antuitrin-S daily into the subcutaneous tissue of the thighs for thirty days (3,000 units). If no results are obtained before this time, the patient is observed every month for three months and then every three months. Some of the cases in which no results were obtained have been followed for two years.

Thirty patients with 36 undescended testes have been treated to date with antruitin-S in this clinic. The ages of the patients varied from 4 to 24 years. The testes were bilaterally retained in 6 instances. Two of the patients with bilateral cryptorchidism also had hypospadias; in a third patient with bilateral cryptorchidism and in a patient with testes inguinally retained there was a suggestion of Fröhlich's syndrome. In 5 patients the retained testes responded to the treatment by degrees of descent into the scrotum. The descent in 3 was complete; the descent in the other 2 was only to a high scrotal position. The latter patients were older, and both later submitted to orchiopexy. One of these patients received a total of 6,000 units over a period of two months. It is interesting that when the patient later submitted to orchiopexy no spermatozoa were seen in either the biopsy or the examination of the smear. Also, the microscopic section of the testis showed the usual atrophic appearance.

No untoward results following the use of antuitrin-S in this clinic have been observed over a period of two years. Three patients had suprapubic edema, which disappeared after treatment. Another patient complained of swelling in the left breast, which clinically was thought to be fibrous mastitis. In none was there a demonstrable increase in the size of the penis. The testes of the successfully treated patients often enlarged; I could not be sure that there was any change in size of the testes of the unsuccessfully treated patients. One boy showed a red and slightly edematous appearance of the scrotum when 2,000 units of antuitrin-S had been administered. In none of the patients was there premature appearance or increase in the amount of pubic, axillary or facial hair. Five patients noticed increased frequency of erections.

Follutein. Two patients, aged 21 and 23 years, were treated with follutein for undescended testes. One patient had bilateral inguinal testis; the other had the right testis inguinally arrested. One cubic centimeter (125 units) of follutein was injected into the subcutaneous tissue of the thigh daily for ten days (1,250 units). No improvement was noted; the patients were observed for a period of one year.

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4. Antuitrin-S and follutein are preparations of the gonadotropic substance from the urine of pregnant women. Prephysin is an extract of the anterior lobe of the pituitary gland. A. P. L. contains gonadotropic substance derived from the placenta.

Prephysin. Three patients, aged 2, 7 and 11 years, were treated with prephysin. All three had unilateral inguinally retained testis. The two younger boys were brothers. Prephysin contains the follicle-stimulating principle of the pituitary gland, including small amounts of luteinizing factor. It differs from antuitrin-S and follutein in that it is extracted from the pituitary gland itself and not from the urine of pregnant women. Each boy was given 2 cc. of prephysin (1 cc. is equivalent to 25 units), 0.5 cc. being injected into the subcutaneous tissue of a thigh daily for four days. No descent of the testis was observed in any of these boys over a period of nine months.

A. P. L. ("Anterior Pituitary-Like Substance"). To date 4 patients have been treated with this substance, which is extracted from placental tissue. The special strength solution, 500 units per cubic centimeter, has been used in doses of 0.5 cc. every other day until fifteen injections have been given. Three patients with unilateral inguinal testes have been treated with this substance and observed less than five months. No beneficial results have been noted to date. However, in the fourth patient, a boy 9 years old, with bilateral inguinal testes, complete descent of both testes occurred after the ninth injection.

Thus, in summary, one may state that of 36 patients with undescended testes who were treated with gonadotropic substances and followed six months or longer, degrees of descent were noted in 6 (16 per cent). In 4, descent was complete. It is possible that the dosage and period of injection of gonadotropic substances in these cases were not adequate, but these factors are comparable to those reported in the successfully treated cases in the literature (Hardy, Bigler and Scott; Cramer).

Evaluation of the Treatment of Ectopic Testis with Gonadotropic Substance.—Rubenstein in the following statement has summarized the current concept regarding the use of gonadotropic substances in the treatment of undescended testis. The water-soluble fraction of the urine of pregnant women seems to produce testicular descent only if the pituitary gland is underdeveloped from the standpoint of the production of the gonadotropic hormone. The injection of this fraction then leads predominately to a stimulation of the interstitial cells of the testicle, and if a mechanical block does not exist, may result in descent.

Nearly all the patients with cryptorchidism who have been operated on at the University Hospitals have shown evidence of mechanical arrest of testicular descent. The testes were often lodged in pockets or bound down by adhesions to such an extent that it was with great difficulty that they were freed or the spermatic cord lengthened sufficiently by loosening adhesions. It is almost inconceivable how one could bring such testes into the scrotum without surgical measures. MacCollum pointed out that it is incongruous to suppose that at some time this fibrous tissue will disappear and allow the testicle "to drop like a plummet" into the scrotum. In my series, 5 patients with undescended testes who had been treated with antuitrin-S (total 3,000 units for each except a patient who was given 6,000 units) submitted to operation

three to six months later. The same degree of fibrous adhesion and mechanical arrest seemed to be present in these as in patients who had not been treated with gonadotropic substance prior to operation. The mechanical obstruction to spontaneous or induced testicular descent as revealed by operation seems adequate explanation of the failure of therapy employing the aforementioned gonadotropic factor.

One wonders if many of the successful results reported in the literature as following endocrine therapy were not obtained in cases of physiologic ectopy and not in cases of true undescended testis. It may be that the gonadotropic substance obtained from the urine of pregnant women is valuable in the treatment of physiologic ectopy, but it should be remembered that in such cases the testes often descend spontaneously. It is not to be inferred that I believe that all the reported cases of retained testes that have descended after a course of endocrine therapy were cases of physiologic ectopy. However, because of the results obtained with this therapy at this clinic and because of the existence of mechanical causes for testicular arrest in most of the cases in which operation was performed, it is believed that endocrine imbalance alone does not fully explain the cause or give a rational basis for treatment in all cases of true testicular maldescent.

There can be no doubt that in some cases of cryptorchidism gonadotropic substances will cause descent of the testis into the scrotum; in others endocrine therapy is of no value and only surgical treatment will remedy the aberrant position of the gonad. In a third group, testicular descent or size may be enhanced by the preoperative or postoperative use of glandular substances. Just what percentages of undescended testes fall in the aforementioned classifications is unknown. However, a method that gives the patient any chance of avoiding a surgical operation certainly merits trial; hence, the use of endocrine therapy at least as a preliminary form of treatment seems indicated.

Suggested Plan of Treatment for Undescended Testis.—It is known from the experiments of Moore and Wangensteen that the testis must be in the scrotum before spermatogenesis occurs, or degenerative changes will set in. Puberty in the male occurs between the ages of 13 and 15 years, without regard to race, climate or individual differences (Spangaro), the extremes being 9 (Scammon) and 18 years (Crampton). Therefore, treatment of the congenitally retained gland may be deferred until the patient is 9 to 11 years old. If no complications are present, there is no objection to operating on a patient with retained testis at any earlier age, but it is unnecessary. The presence of a large associated hernia may necessitate earlier surgical intervention, since an undescended testis precludes the use of a truss and injection of a sclerosing solution in the treatment of inguinal hernia. It is the practice at the University Hospitals to suggest first a trial of the gonadotropic

substance obtained from the urine of pregnant women in all uncomplicated cases of undescended testes before surgical procedures are undertaken. Possibly the determination of gonadotropic substance in the urine before treatment (Hess and others) will aid in the selection of patients for this treatment. It would be of practical value to know before treatment whether there are mechanical causes for the testicular maldescent, but unfortunately no way to determine this is known. There are various methods of administering endocrine therapy. While the available gonadotropic substances are well standardized, the doses and intervals of injection prescribed by various authors are rather empiric. At this clinic the methods of treatment outlined in a foregoing section are still followed, except that greater doses are given in some instances, as well as subsequent courses of injections, at two to three month intervals, if the patient is under 9 years of age. I have had no experience with extremely large doses of gonadotropic substances in the treatment of cryptorchids at this clinic, as the cost is prohibitive. If after six months of observation no results have been observed from endocrine therapy, surgical treatment of the undescended testis is advised if the patient is 9 years old or older.

In résumé the following points should be reemphasized: Treatment of the retained gonad may be deferred until the patient is 9 to 11 years old. Reports in the literature on cryptorchids treated by gonadotropic "hormones" reveal that in as high as 70 per cent there is descent of the testes into the scrotum. With the hope that the case may be a favorable one, a course of treatment with the gonadotropic substance obtained from the urine of pregnant women may be tried first. This form of therapy has not been as efficacious in the cryptorchids treated to date at this clinic, degrees of descent being obtained in only 16 per cent of the patients so treated. No untoward effects resulting from such therapy have been observed.

For reasons mentioned elsewhere, it is believed that endocrine imbalance alone does not fully explain the cause or give a rational basis for treatment in all cases of true testicular maldescent. However, a gonadotropic substance should be given at least a preliminary trial in the treatment of undescended testis, and if no results are obtained an orchiopexy should be performed.

V. SUMMARY

The causes of failure of the testes to descend are unknown, but endocrine imbalance is probably one of these factors. Undescended testes do not differ grossly or histologically from the normal up to puberty, but after this they undergo degenerative changes. Just how long the undescended human testis remains capable of function is unknown, but there are undoubtedly isolated cases in which spermato-

genesis has persisted into adult life. In this study, smears of cut sections of abdominal testes occurring naturally in adult pigs not infrequently showed spermatozoa. The superiority of the smear over the microscopic section of the testis in determining the presence of spermatozoa has been shown.

From a review of the literature, it seems established that most undescended testes have an internal secretion and occasionally may possess an external secretion sufficient for potential, if not absolute, fertility. It is estimated that 10 per cent of untreated human cryptorchids remain fertile.

It has been proved clinically that as high as 82 per cent of those treated by orchiopexy have active spermatozoa in the semen. Placing the slightly atrophic or immature retained testis of man or of the pig into the scrotum has been shown experimentally to permit the germinal epithelium to mature. The degree of maturity after orchiopexy for natural failure of descent is never as great as that seen after the same treatment in the case of experimentally produced cryptorchidism. However, clinically and experimentally the value of orchiopexy for promoting maturation of the germinal epithelium has been demonstrated beyond doubt.

Various preparations of the gonadotropic substance have been used clinically and experimentally at this clinic to cause descent of the testes into the scrotum. The indications for and limitations of such therapy are as yet in an empiric stage. Proof is lacking to date that this form of therapy will cause germinal maturation in the naturally cryptorchid testis. That serum from pregnant mares may maintain the normal histologic appearance of the testis in spite of an aberrant position of the gland has been suggested from experimental investigations. In this study, the hypophyses of 5 pigs with naturally occurring retained gonads failed to show any castration cells. The gonadal-pituitary relation is probably more labile than is generally believed. The relative importance in the function of the testis of the scrotal (thermoregulatory) hormonal balance has not been established.

Judging from the number of spermatozoa in the ejaculated semen as well as from the histologic appearance of the undescended testis after orchiopexy, such organs probably never attain an entirely normal functional capacity. Whether the potential function of the ectopic testis is inherently smaller than that of the descended gland is unknown. Histologic examination up to the time of puberty and the results of tissue culture fail to show any positive proof of congenital imperfection. Most of the imperfections become apparent at puberty, probably as the result of the influences of hormonal and of extrinsic anatomic factors arising at that time.

The following findings also seem established:

1. Failure of the testis to descend should not be considered a precancerous condition.

2. Treatment of the undescended testis may be deferred until the ninth to eleventh years. Treatment with a gonadotropic substance may be tried first, but if no results are apparent within six months orchiopexy should be performed.

3. Obstruction to the pathways for seminal transmission does not result in permanent testicular degeneration.

4. In the dog with experimentally produced cryptorchidism the increase in the interstitial tissue of the testis is relative and not absolute.

5. The observations on natural cryptorchids parallel in general those on animals in which cryptorchidism was experimentally produced.

VI. CONCLUSION

The undescended testis, either untreated or after orchiopexy, never attains the full functional capacity of the normally descended organ as far as the production of spermatozoa is concerned. However, the value of orchiopexy in promoting the development of the undescended testis has been proved clinically and experimentally in both natural and experimentally produced cryptorchids.

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ROUTES OF ABSORPTION IN TOTAL
URETERAL OBSTRUCTION

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A previous contribution [1] on the routes of absorption in the presence of hydronephrosis, based on experiments with molecular dyes and colloidal preparations, demonstrated that there are two routes of absorption, lymphatic and tubular. In the previous investigation, at the onset of complete ureteral obstruction there ensued for about two or three days a purely lymphatic absorption from the walls of the renal pelvis and the ureter. After approximately the third day a tubular absorption began, and this continued more actively than the lymphatic absorption. It was noted that the distal convoluted tubules of the peripheral layer of glomeruli were the first to assume this function, and as pressure atrophy progressed the subjacent tubule layers, seriatim, continued the process. The cells of the convoluted tubules by thus absorbing the mediums demonstrated a slightly altered function and one of definite significance in renal pathology.

Throughout the investigation care was taken not to strain the pelvic capacity but to inject an amount of dye less than the pelvic contents as shown by aspiration. As a result of misjudgment of the capacity in 2 instances, overdistention occurred, and as a result of pyelovenous back flow, dissemination of the dye into the general system was observed, reticuloendothelial cells of the liver and spleen showing obvious presence of the dye. Apart from these 2 instances no evidence of absorption into the general system was found throughout the investigation.

As it was felt that this failure was probably due to the comparatively large molecular values of the mediums employed, it was decided to continue investigation with other agents and to observe whenever possible the actual process of absorption in the living tissues.

1. Morison, D. M.: Routes of Absorption in Hydronephrosis: Experimentation with Dyes in the Totally Obstructed Ureter, Brit. J. Urol. 1:30-45 (March) 1929.

The following experiments were undertaken:

1. To determine by their elimination from the healthy kidney the rate of absorption from the hydronephrotic sac of agents routinely employed in the estimation of renal function.

2. By similar procedures to those previously adopted to study the routes of lymphatic absorption from the obstructed pelvis.

3. By direct observation of the normal and the obstructed ureter and kidney to determine the rate and routes of lymphatic absorption after intramural and parenchymal injections of dye.

4. By direct observation to note the rate and mode of absorption of dye from the lumen of (*a*) the ureter and (*b*) the renal pelvis.

5. To study the lining epithelium of the upper part of the ureter and the renal pelvis after vital staining.

To obviate unnecessary repetition, the two main operative procedures employed as a preliminary to a number of the group experiments are described here and are briefly referred to subsequently as operation A and operation B (fig. 1).

TECHNIC AND OPERATIVE PROCEDURES

The animals used were rabbits under open ether anesthesia.

Operation A.—Through a midline suprapubic incision, the left ureter was identified at the bladder and divided between ligatures. The wound was closed. The animals were kept thereafter for varying periods as desired, with total obstruction of the left ureter.

Operation B.—On expiration of the desired period of hydronephrosis the animal was again anesthetized with ether, and the suprapubic wound was reopened and continued up to the epigastrium. The abdominal contents were then packed off so as to expose completely the left kidney and its pedicle, together with the entire length of the obstructed ureter.

When it was desired to introduce dye into the ureteral lumen and maintain hydronephrosis in order to observe absorptive changes in the kidney and ureter, the following procedure was carried out:

The lower end of the obstructed ureter was mobilized, and two ligatures were so placed that the upper one was left with a loose single knot and the lower one was tied at once and used for traction. Between the two ligatures the ureter was sufficiently opened to admit an F 4 ureteral catheter; on this the loose upper ligature was sufficiently tightened to prevent leakage of contents. To obviate trauma of the ureteral epithelium the catheter was advanced gently as far as the pelvoureteral level, and aspiration of its contents was done. Particular care was taken in each instance, as before, to introduce a quantity of medium less than the amount of contents aspirated. After the injection the previously tightened ligature was firmly tied on the ureter as the catheter was withdrawn. Measures were taken to preclude any leakage of dye.

RATE OF ABSORPTION FROM THE HYDRONEPHROTIC SAC

Since intravenous pyelographic mediums and dyes are routinely employed for the estimation of renal function, uroselectan B (known in the United States as neo-iopax), phenolsulfonphthalein and indigo carmine suggested themselves.
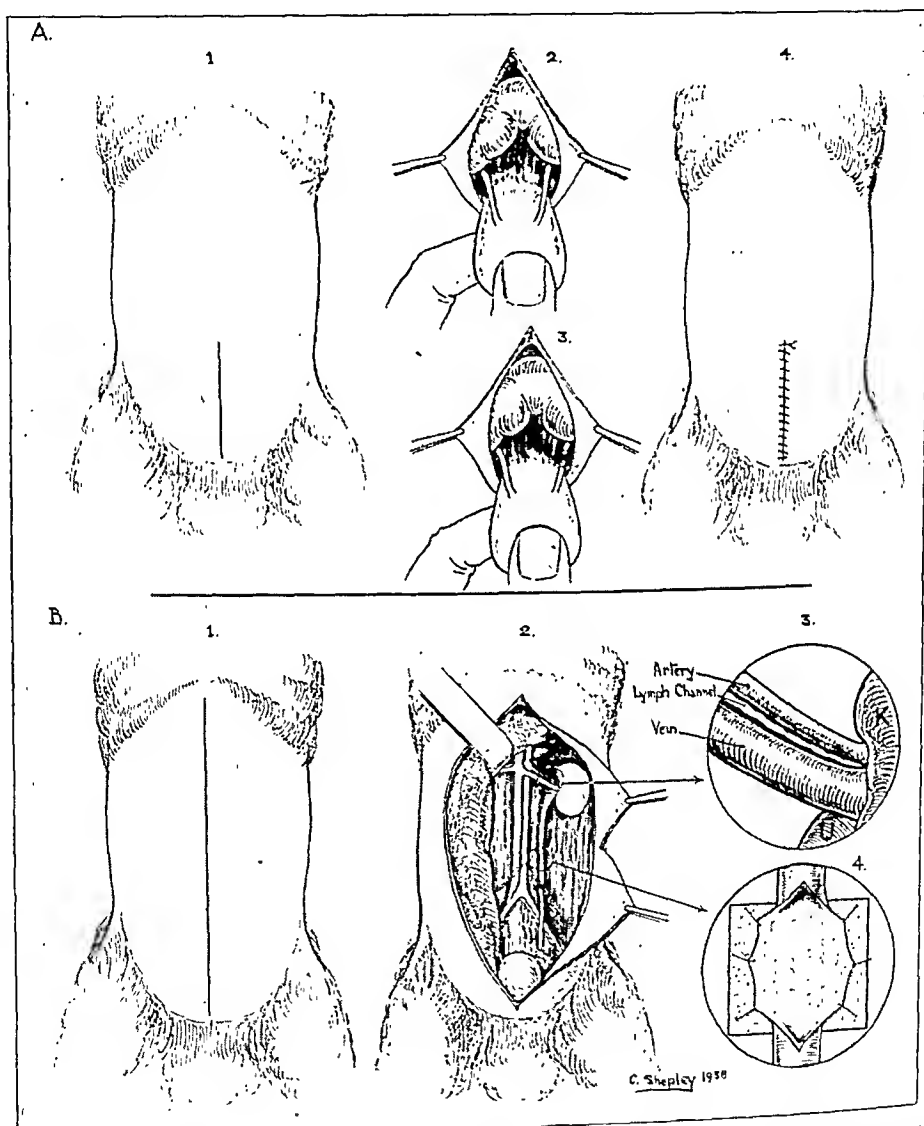
Fig. 1.—Operative procedures: *A*, ligation of the left ureter, showing (*1*) the incision, (*2*) the bladder displaced downward to expose the ureters, (*3*) the left ureter divided between ligatures and (*4*) the wound as closed. *B*, complete exposure of the left kidney and ureter, showing (*1*) the incision, (*2*) the abdominal contents packed off, with exposure of the left kidney and ureter, (*3*) a detail of the renal pedicle, and (*4*) a segment of the ureter prepared for study of the lining epithelium.

Clinical Studies.—A small number of clinical cases of unilateral hydronephrosis was studied by the introduction of uroselectan B into the affected side after partial or total aspiration of the contents. If

ureteral spasm followed withdrawal of the catheter, it was noted by serial roentgen studies that in about thirty minutes after introduction of the opaque medium into the hydronephrotic sac the parenchymal outline of the opposite, healthy kidney began to manifest itself, and presently a definite pyelogram of this side appeared (figs. 2 and 3).
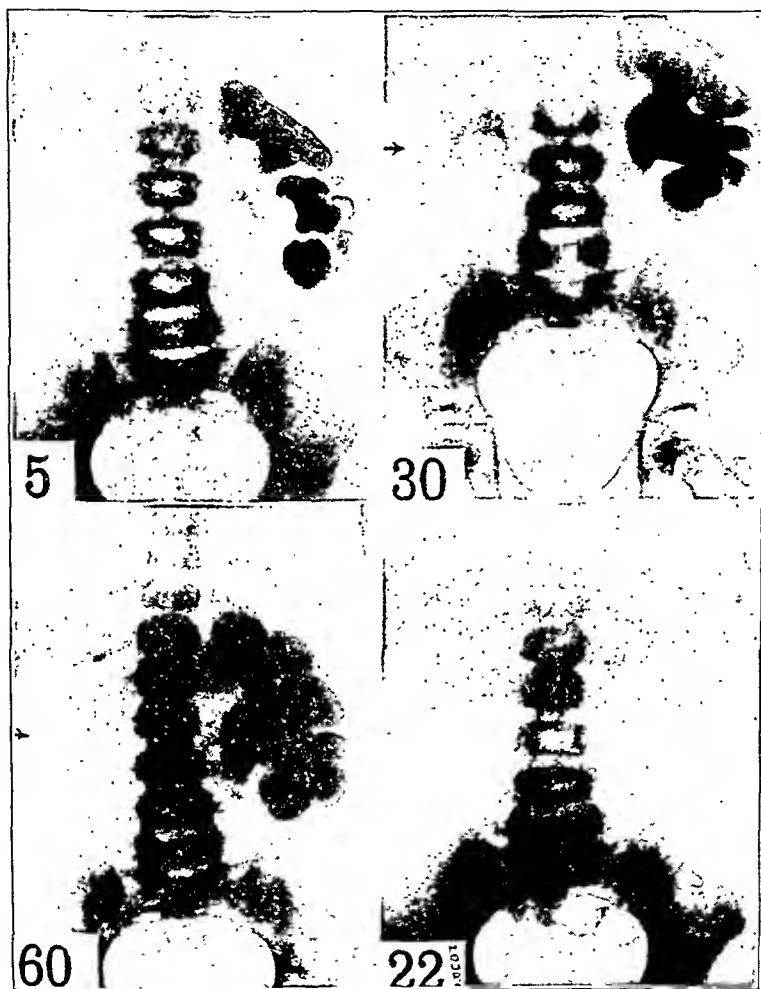
Fig. 2.—Congenital unilateral hydronephrosis. The serial pyelograms were taken five, thirty and sixty minutes and twenty-two hours after introduction of uroselectan B into the hydronephrotic sac. The films taken at thirty and sixty minutes show by reabsorption from the affected side a faint but definite pyelogram of the opposite, healthy kidney.

Experimental Studies.—As it was desired to obtain more detailed data as to the mode of absorption of the opaque medium from the hydro-

nephrotic side into the general system (as proved by its elimination from the opposite, healthy kidney), a series of similar studies was carried out on rabbits at varying periods after total ureteral obstruction. The data obtained were not sufficiently convincing, though similar to those obtained from studies on man. In some instances, however, the cortical

Fig. 3.—Congenital left hydronephrosis with hydroureter. The serial pyelograms were taken immediately and three, thirty and seventy-five minutes after the introduction of uroselectan B into the affected side. In thirty minutes after pelvic and ureteral capacity has been reestablished the pyelogram of the right kidney begins to show the dye.

zone of the hydronephrotic side revealed a radial increased density prior to the appearance of the opaque medium in the bladder from the unobstructed side.

To determine whether absorption took place by way of lymphatic or venous routes, comparative determinations were made on animals both with and without prior interruption of the main lymphatic channels of the renal pedicle. Before, and at intervals during, the period of absorption of the medium from the hydronephrotic side, samples of blood were drawn off from the renal vein and subsequently studied roentgenographically. None of the samples showed any evidence of variation in density.

The findings in relation to indigo carmine and phenolsulfonphthalein were as follows: After injection into the veins of the ear the former dye appeared in the vesical urine in ten minutes and the latter in barely two minutes. When introduced into the hydronephrotic sac, phenolsulfonphthalein usually appeared in the bladder by excretion from the healthy side in about one hour, whereas indigo carmine in most instances did not show for four hours or longer.

The effect of lymphatic interruption at the renal pedicle was tried in a small number of animals. It did not appear to influence in any way the rate of appearance of either of the dyes used. Similarly, the preliminary administration of 20 cc. of physiologic solution of sodium chloride intravenously as well as 20 cc. subcutaneously did not materially alter the time of appearance of these dyes.

ROUTES OF LYMPHATIC ABSORPTION FROM THE OBSTRUCTED PELVIS

As pontamine sky blue is regarded as having an affinity for lymphatics, this dye was employed in a series of animals in a manner similar to that adopted in the original published investigation, in which berlin blue (aniline blue), pelican ink and other medicines were used. The studies revealed no additional information regarding the routes of lymphatic drainage. Tubular absorption was depicted as clearly as with the other dyes.

RATE AND ROUTES OF LYMPHATIC ABSORPTION AFTER INTRAMURAL AND PARENCHYMAL INJECTIONS OF DYE

The work of previous investigators on the lymphatic system has shown that the rate of absorption in certain regions is rapid, particularly from the ovary, the testis and the cervix. Similarly, dyes injected into the superficial aspect of the renal parenchyma around the hilus are quickly absorbed and are soon evident in the main lymphatic channels of the renal pedicle. It was felt, accordingly, that fresh data might be obtained if the process of absorption was carefully watched under the binocular microscope during life.

At the outset, small quantities of pontamine sky blue were injected under binocular control with a fine needle into the ureteral wall at different levels. Ureters that had been obstructed for various periods were studied and compared with the normal ureter. No dramatic evidence of lymphatic absorption could be detected at the time of injection or for two to three hours subsequently, despite continuous observation. Similar procedures applied to the superficial zones of the renal cortex disclosed at times a definite intratubular distribution of dye, the affected tubules taking on the same appearance as in absorption. With such injections the lymph channels of the pedicle showed no dye content. At other times the injected dye entered only the intertubular spaces and graphically showed up, in contrast, the arrangement of the superficial tubules. In these instances, within a space of one or two minutes the pedicle lymphatics disclosed an easily discernible dye content. It has been stated that dye injected into the renal parenchyma near the hilus readily finds its way into the pedicle lymph channels, but the aforementioned tests, which gave similar results, were carried out on the outer border of the kidney, well away from the hilus.

RATE AND MODE OF ABSORPTION OF DYE FROM THE LUMEN
OF THE URETER AND THE RENAL PELVIS

(a) *Absorption from the Ureteral Lumen.*—Several dyes, i. e., pelican ink, lampblack, janus black, gentian violet and pontamine sky blue, were employed. After repeated experiments, however, it was found that pontamine sky blue in 2 per cent and 5 per cent freshly prepared aqueous solution was the most satisfactory. The dye was introduced into the ureters, which had been totally obstructed for periods varying from a few minutes to four or five weeks.

From the surface no evidence of dye passing along the lymph channels could be detected. As in these experiments the renal changes also were being watched, the animals were killed at periods varying from two to twelve hours after introduction of the dye. After fixation for twenty-four to forty-eight hours the ureters were divided at the renal pelvis, longitudinally opened and pinned out on cork (fig. 4). A gentle stream of water was used to remove any free dye remaining. Microscopic study of the ureters from their mucosal surface usually revealed a mixed grouping of cell types over different areas (fig. 5). There appeared to be a patchy distribution of absorption. Here and there, large flat transitional epithelial cells were present in irregular groups, but most areas showed smaller forms, apparently of a subjacent layer, with relatively larger nuclei and arranged occasionally in bands and whorls. In patches at a deeper layer, closely packed small rounded

cells could be seen. These took the dye more faintly and proved to be the so-called pear-shaped cells.

The impression gained from this study was that through instrumentation and handling a considerable degree of derangement of cells had occurred and that it would be advisable to observe the action of dye applied directly to the exposed, living ureteral epithelium.

Action of Dye on Living Ureteral Epithelium: By means of operative technic B the ureter was observed in segments, the procedure being started with the lower end and repeated almost as far as the renal pelvis. The selected ureteral site was mobilized by incising the peritoneum on
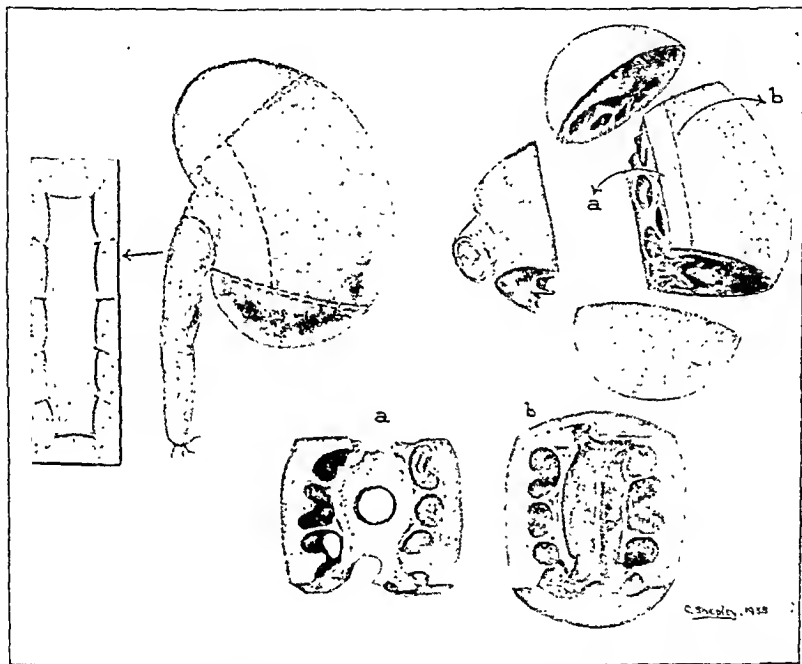
Fig. 4.—Procedure adopted in preparation of the fixed specimen for study. Freehand or frozen sections may be made subsequently as desired.

the outer side and displacing it medially. A small, thin piece of cork covered with white paper was slipped under the freed segment. The portion of ureter over the cork was incised longitudinally to a sufficient extent to enable a flat field of ureteral lining to be exposed by gentle retraction. In fixing the margins to the underlying cork by fine pins, care was taken to avoid any tension that would impair circulation. Under direct binocular control a very small drop of dye was placed gently on the epithelial surface and was watched. The changes observed were as follows:

As the dye began to spread, it appeared to pass into a network of fine channels with clear interspaces. The spaces were fairly uniform in size but varied in shape, the majority being pentagonal or hexagonal. After a few minutes this fine, apparently intercellular network tended to be obscured by a subjacent spread of diffuse dye into well defined areas with angulated margins. After a few more minutes points of intenser staining appeared throughout this area, and presently there was revealed a pavement type of epithelium with clear spaces between the
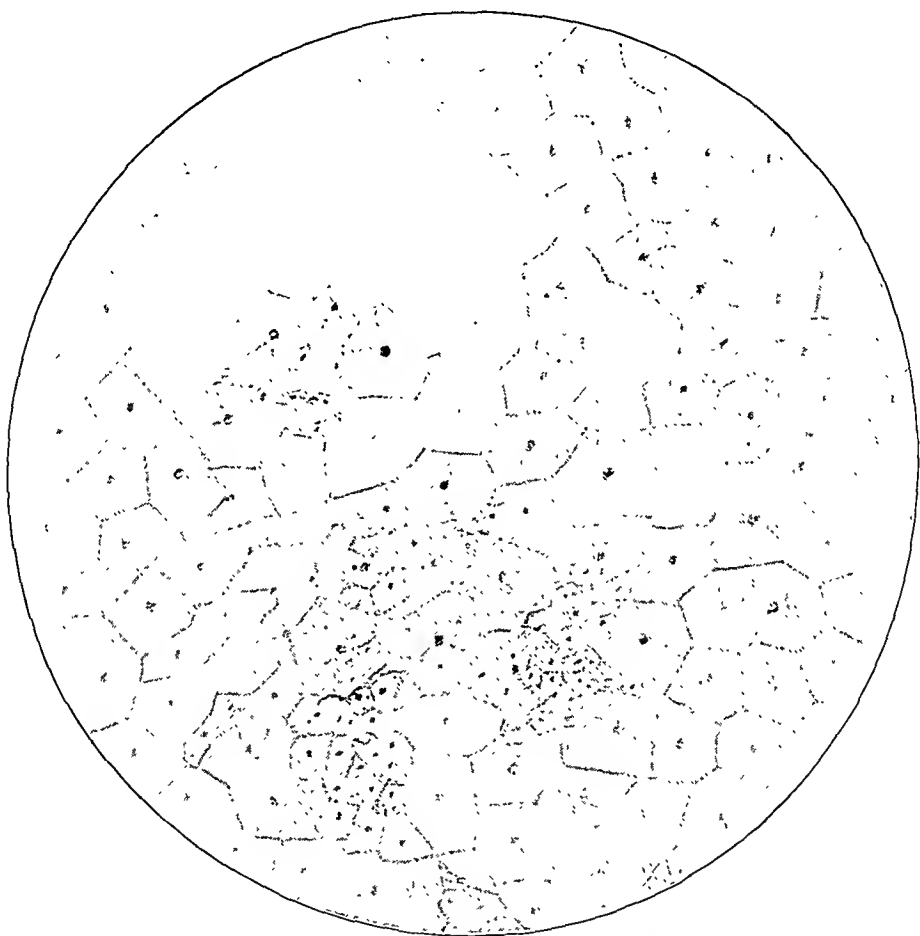
Fig. 5.—Ureteral epithelium in total obstruction. This is a composite drawing of the altered cellular arrangement as viewed from the surface. The oldest and most superficial transitional cells, not having absorbed dye or having absorbed it only faintly, show up clear with pale nuclei. They tend to preclude dye from penetrating to underlying cells. From areas where these cells have desquamated, varying intensity of absorption occurs. The youngest generation of small, flat cells takes a relatively deep stain. A number of the large cells have a stellate appearance, caused by the presence of subjacent small rounded cells.

cells and well stained large nuclei, some of which were double. Variation in the size of these cells was noted, in that as diffusion of the dye continued relatively smaller ones became evident. Subsequently, scattered

areas of densely packed, small rounded cells could be seen. These absorbed the dye rather faintly and were about a third the size of the epithelial cells previously described.

To determine the relation of these cell types a small pledget of cotton wool moistened in saline solution was gently applied to the well defined original network. Instantly there occurred a desquamation of clear cells, obviously a keratinous layer. After the removal of this layer, the staining of the subjacent layer was more rapid, the intercellular spaces soon showing as a clear, roughly hexagonal-meshed network against the deeply stained cells of the transitional epithelium. When drops of physiologic solution of sodium chloride were gently applied to this layer of cells, it was noted that individual cells easily became detached and floated away. When one continued to remove these cells and apply fresh dye, the small rounded cells became evident. This layer was more firmly fixed and could not be detached with anything like the ease with which the first two layers were detached.

(*b*) *Renal Absorption.*—In animals with total obstruction of the left ureter for periods varying from a few minutes to a month or more, the left kidney and ureter were exposed as described for operative technic B. Ether was first given, and narcosis was maintained as required by injections of pentobarbital sodium. Some of the observations were continued at intervals for a total period of twelve hours.

Immediately after introduction of the dye into and religation of the ureter, observation was centered on two sites: (*a*) the lymph channels of the renal pedicle and (*b*) the surface of the kidney.

(*a*) By removing the peritoneal covering and gently separating the components of the renal pedicle one can identify the lymph channels. The lymph vessel, with its translucent walls through which the fine bicuspid valves can readily be seen, is a characteristic structure. At the pedicle the lymph channels vary in number and manner of distribution but are as a rule associated with the renal artery and lie between it and the vein.

As a precautionary measure, simultaneous dual observation was made with one binocular microscope trained on the lymph vessels of the pedicle and another focused on the surface of the kidney. It was hoped that in this way any rapid temporary transit of dye through the lymph channels would be detected.

(*b*) In the presence of hydronephrosis the lymph channels coursing over the surface of the kidney in the false capsule appear to be somewhat more distended and easier of identification than in the normal kidney. During the initial period after the introduction of dye these capsular lymph channels were watched for any evidence of conveyance of the dye, and the renal cortex was coincidentally observed for tubular

absorption.   As tubular absorption is patchy in distribution it was necessary to be constantly reviewing a large surface of cortex, particularly the middle third zone, in which the absorption occurs more frequently.   The first evidence was mottled pallor around certain groups of renal lobules.   Looking down on the surface, one could usually discern the terminal end of a main collecting duct in the center of one of these paler lobules.   It showed as a small rounded dot.   It became more pronounced because of ascending dye in its lumen, and presently its terminal subdivision into two or more irregularly arched connecting and distal convoluted tubules was made visible by the contained dye.   An area showing a group of absorbing tubules presented the appearance below the true renal capsule of an irregular cluster of uneven, inverted U-shaped bends (fig. 6 *a*).   Owing to a number of easily appreciated factors, i. e., the degree of diuresis, the amount of dye introduced in relation to the total pelvic content, the degree of reduction of pelvic content after interference and the period of total obstruction, the time of appearance of dye in the tubules varied.   In 2 instances it appeared within ten minutes.   In the average obstruction of from five to seven days dye manifests itself in about thirty minutes.   With hydronephrosis of about four weeks' standing the time of appearance is lengthened to approximately one or two hours.

The dye at first seemed to stain the tubule diffusely, but later an intensification of stain appeared at the basement membrane, and individual basal cells could be noted (fig. 6 *b*).   At this stage, small well stained objects, such as granules or portions of cells, were frequently to be seen within the tubules.   At the outset of this study no particular attention was paid to these except to note that they were probably basal cells so situated on the wall of the tubules as to present a surface view. More consistent observation, however, revealed that some of these particles were not stationary as had been assumed.   In a number of instances such particles were observed to ascend into the loop of the tubule, traverse its visible extent and after a short pause return to the starting point.   This excursion was repeated at brief intervals.   The rhythm of these movements was noted and was observed to coincide with the ureteral peristaltic waves, which occurred every thirty to thirty-five seconds.   The impression gained was that in the presence of hydronephrosis the main collecting ducts and their immediate subdivisions, together with the connecting and distal portions of the tubule units, are dilated and are in fluid continuity with the pelvis and ureter.   Thus, alterations in the content pressure of the latter are transmitted directly to the periphery of the renal cortex.

Although it was hoped that it might be possible to observe by transference of dye the mechanism of absorption from the tubule back into

the general circulation, no definite data could be obtained. It was noted, however, that after thirty minutes or so the tissues in the vicinity of tubules which had taken up dye began to show a pale tinge of the dye. This pale coloring appeared to be in the intertubular spaces, but whether in lymphatic or venous radicles it was impossible to say (fig. 6 *c*). At the time of its appearance and subsequently, the lymph channels of the renal pedicle were carefully watched for a possible trace of color in their contents, but without any convincing result.
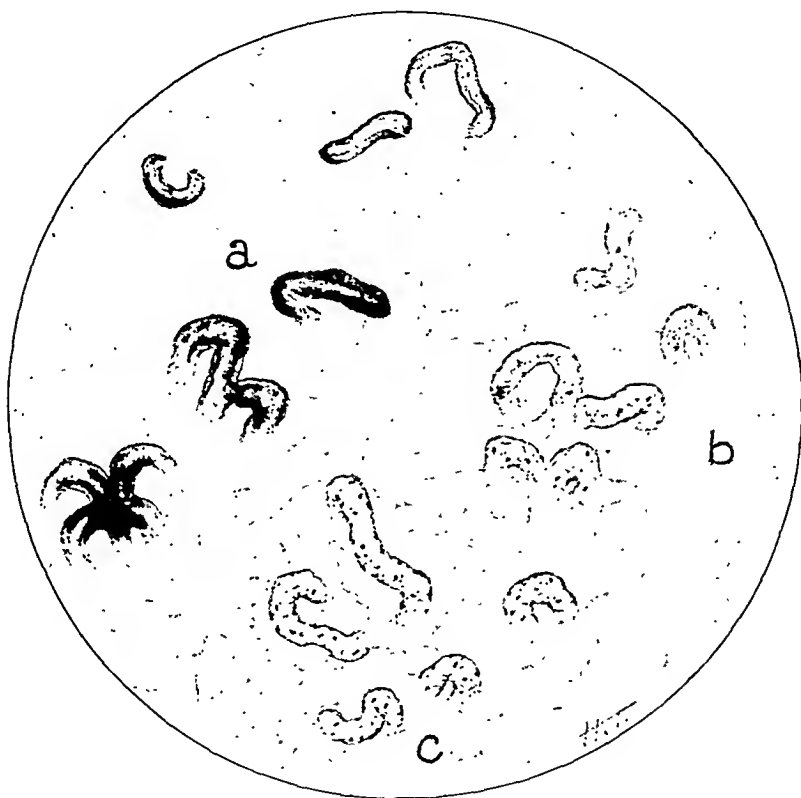
Fig. 6.—Tubular absorption as seen on the surface of the renal cortex. This is a composite drawing of three small groups of tubules at varying stages of absorption of dye. The point marked *a* denotes absorption during the initial period. The tubules show marked content of dye. The point marked *b* denotes absorption during the intermediate stage. The content of dye is less apparent; the tubular walls and the cells are becoming stained. The point marked *c* denotes absorption in the late stage. The lumen of the tubule is almost free of dye, while discrete cells and the walls of the tubule are deeply stained.

As has been indicated, the spleen and a portion of the liver were removed in each instance when the animal was killed. When dyes had been employed, careful study of sections of these organs failed to show any evidence of dye.

LINING EPITHELIUM OF THE UPPER PORTION OF THE URETER
AND THE RENAL PELVIS AFTER VITAL STAINING

Dissections of the rabbit kidney after vital staining and fixation revealed certain interesting features with regard to the lining epithelium of (*a*) the pelvic portion of the ureter, (*b*) the pelvis and (*c*) the papilla.

(*a*) *Pelvic Portion of the Ureter.*—The pelvic portion of the ureter (fig. 7), or that portion which expands within the renal hilus to
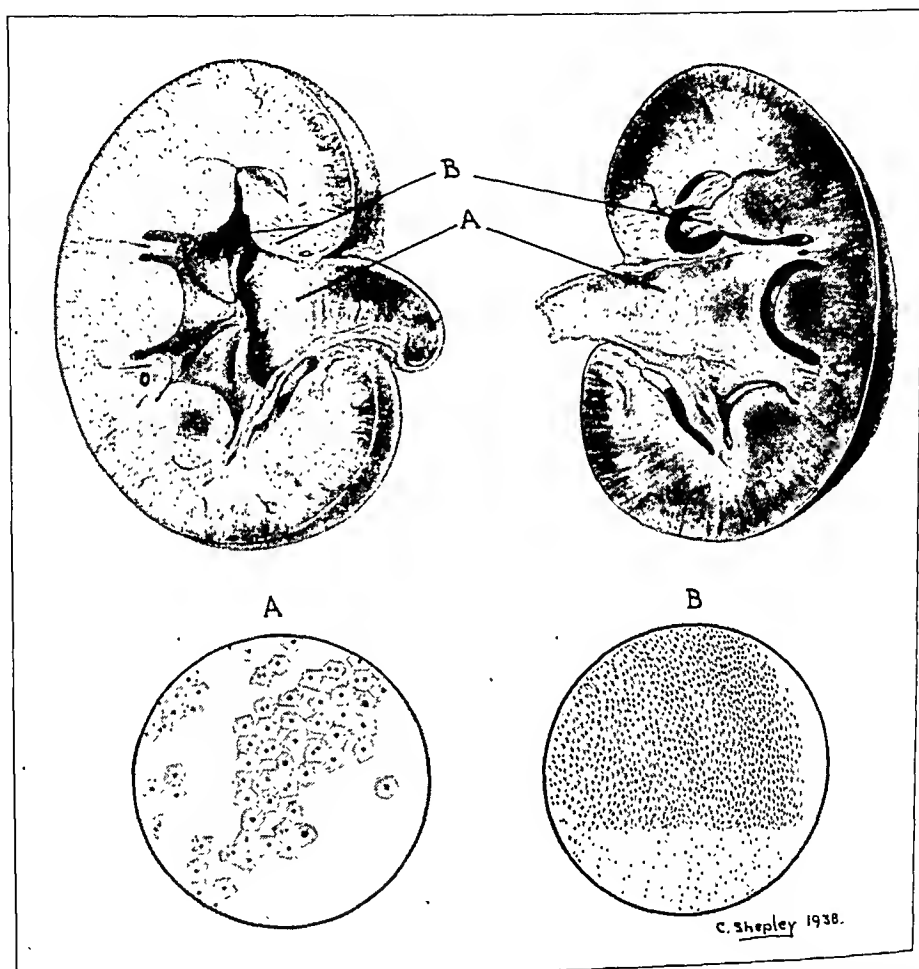
Fig. 7.—Early stage of hydronephrosis (rabbit). The longitudinal section discloses the components of the renal pelvis. *A*, pelvic zone of the ureter. *B*, parenchymal walls. In the circles the types of epithelium characteristic of these areas are correspondingly indicated.

accommodate the papilla and terminates in a fluted manner around the sulcus at the base of the medullary pyramid, has a lining epithelium similar to that of the rest of the ureter. It is capable (probably to a lesser extent than is the ureter proper) of expansion and contraction; consequently, the lining epithelium must be able to meet for a time the extra stress incurred by total obstruction.

After obstruction had been present for about a week or more, the transitional epithelium of the lining was observed to present definite changes. The previously uniform layer of cells showed scattered distribution. The vital staining was taken up by cells individually or in groups, intervening spaces being left completely clear, with no evidence of absorption of dye. The remaining cells usually showed either larger single nuclei than normal or double nuclei (fig. 8 *A*). The stellate appearance not infrequently noted in the normal state was at times pronounced. This suggests that dye had probably passed from the overlying flat cell into the interspaces between the pear-shaped cells underneath. In some specimens taken after long obstruction most of the typical large superficial cells had disappeared, and in their place were
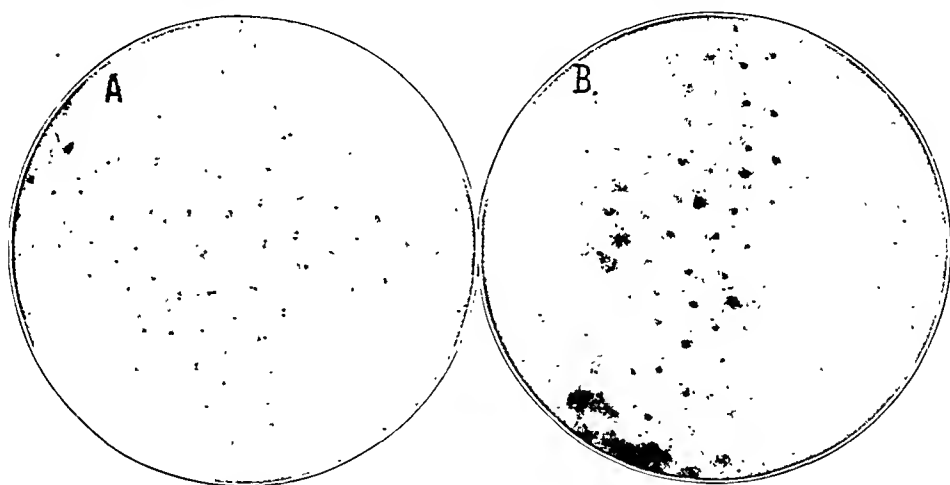
Fig. 8.—Photomicrograph of lining transitional epithelium in a case of total obstruction (surface view). *A*, pelvic zone of the ureter. *B*, ureter.

smaller cells of various shapes (figs. 9 *A* and 9 *B*). These frequently grouped themselves into peculiar whorl formations, spirals or bands (fig. 10).

(*b*) *Pelvis.*—The lining of the pelvic walls (fig. 7 *B*) and the partition-like extensions which unite with the ureteral expansion and enfold the main subdivisions of the renal artery and vein on either side showed a uniform epithelial covering in which an occasional small pear-shaped cell became outlined with dye. This actively absorbing cell was slightly columnar and after becoming stained protruded somewhat from the general surface. It differed from any of the transitional cell types and was much smaller. After vital staining the number outlined was relatively small in the lower aspects of the calices, but such cells appeared to be invariably more numerous in the upper zones and particularly at
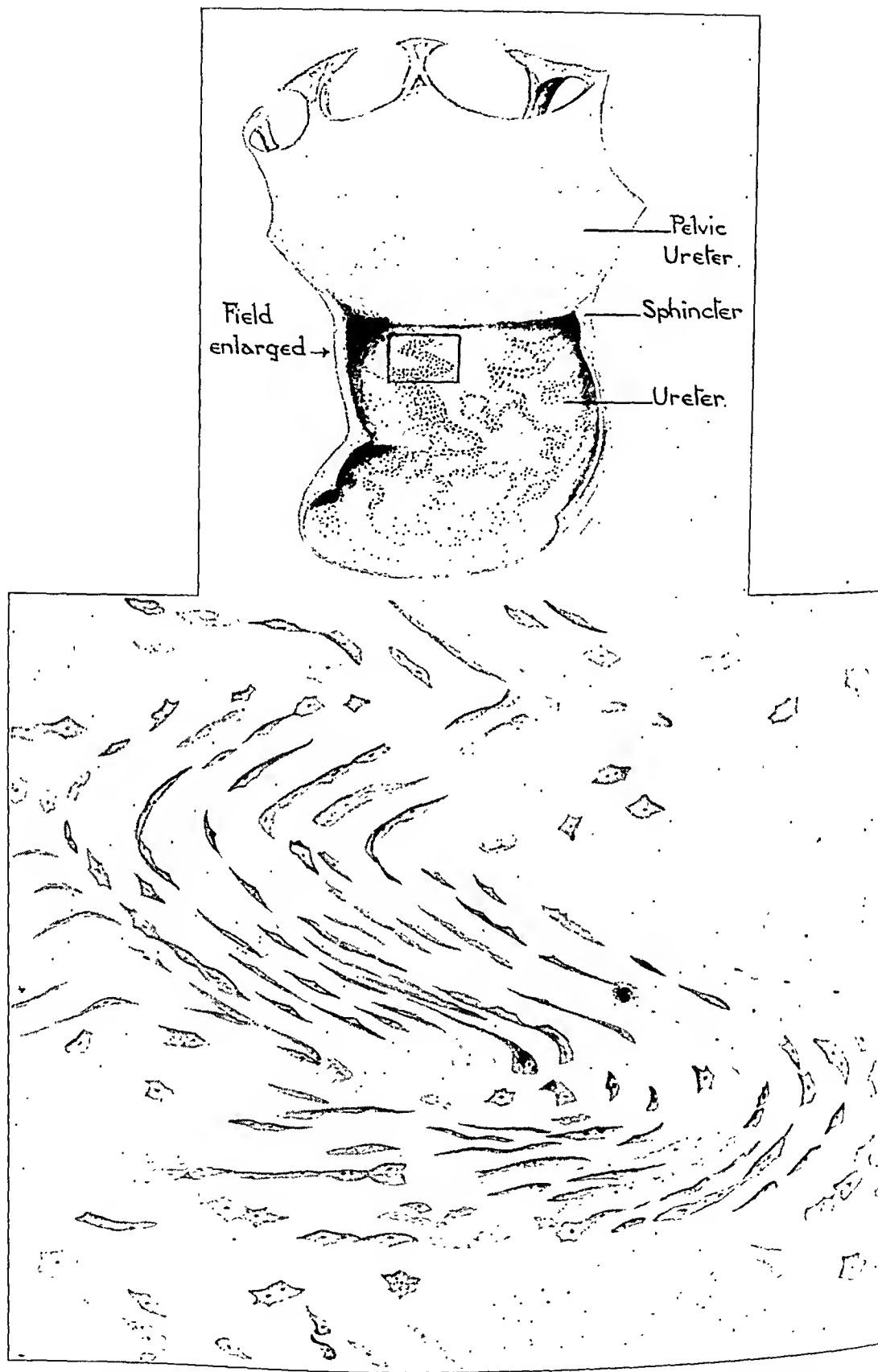
Fig. 9.—*A*, chart to act as a guide to figure 9 *B*. *B*, transitional epithelium at the pelvoureteral zone. Note the derangement consequent on total obstruction. Considerable desquamation has occurred, exposing areas of the faintly staining, small rounded cells of the basic layer. The distortion of the cells is probably due to the abnormal pull exerted by the fibrils which under normal conditions maintain the relation of this type of epithelium despite a considerable range of expansion and contraction.

the angle of reflection, where the lateral walls meet the base of the papilla. In many instances the extent of absorption of dye by the cells in these special sites was intense and usually was associated with infiltration of dye into the subjacent tissues. Despite careful search, no definite evidence has so far been obtained of any lymphatic association, but the picture suggests such a probability.

(c) *Papilla.*—From observations made on a series of renal papillae after varying periods of total ureteral obstruction it is evident that this structure is almost the pivotal point in the distending renal pelvis. It is subject to a progressive outward radial pull, and the consequent tension is liable on any extra stress to cause splitting of the overlying mucosa and even rupture of the papilla (figs. 11 and 12). With vital staining
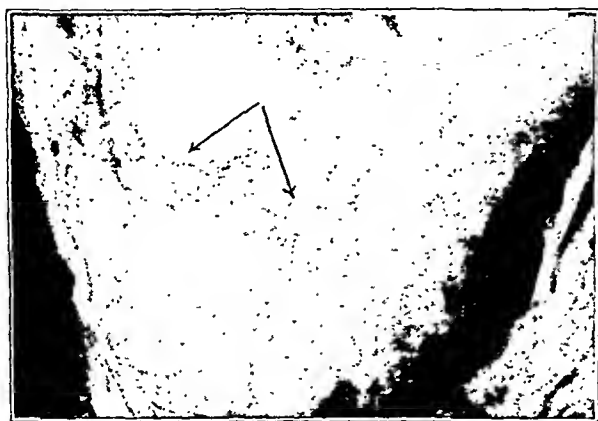
Fig. 10.—Pelvic portion of the ureter. The illustration shows a portion of the wall, surface view. Vital staining was used. The transitional epithelium shows considerable derangement, with a limited group of stained cells forming a wavy band, as indicated.

the epithelium covering the papilla presents points of interest which are not apparent in ordinary paraffin sections. After the specimens were fixed in Jores solution, frozen or freehand sections were made and examined under varying powers of the binocular microscope. By this means it was felt that distortion was minimized and a three-dimensional impression gained of the grouping and character of the cells. The manner of absorption of dye shown by the cells of this particular region tended to strengthen the impression of a definite selective action. Only a certain number of the cells absorbed dye, and those doing so were fully stained, whereas adjacent, apparently similar cells remained clear. The contrast, accordingly, offered greater facilities for observing the type and distribution of the cells.

It was noted that the stained cells covering the papilla were somewhat wedge shaped, with nuclei toward the broad end. They were arranged in a definite columnar fashion, particularly at the summit, around the openings of the main collecting ducts (fig. 13). From the summit the length of the cells gradually lessened, and as the papillary
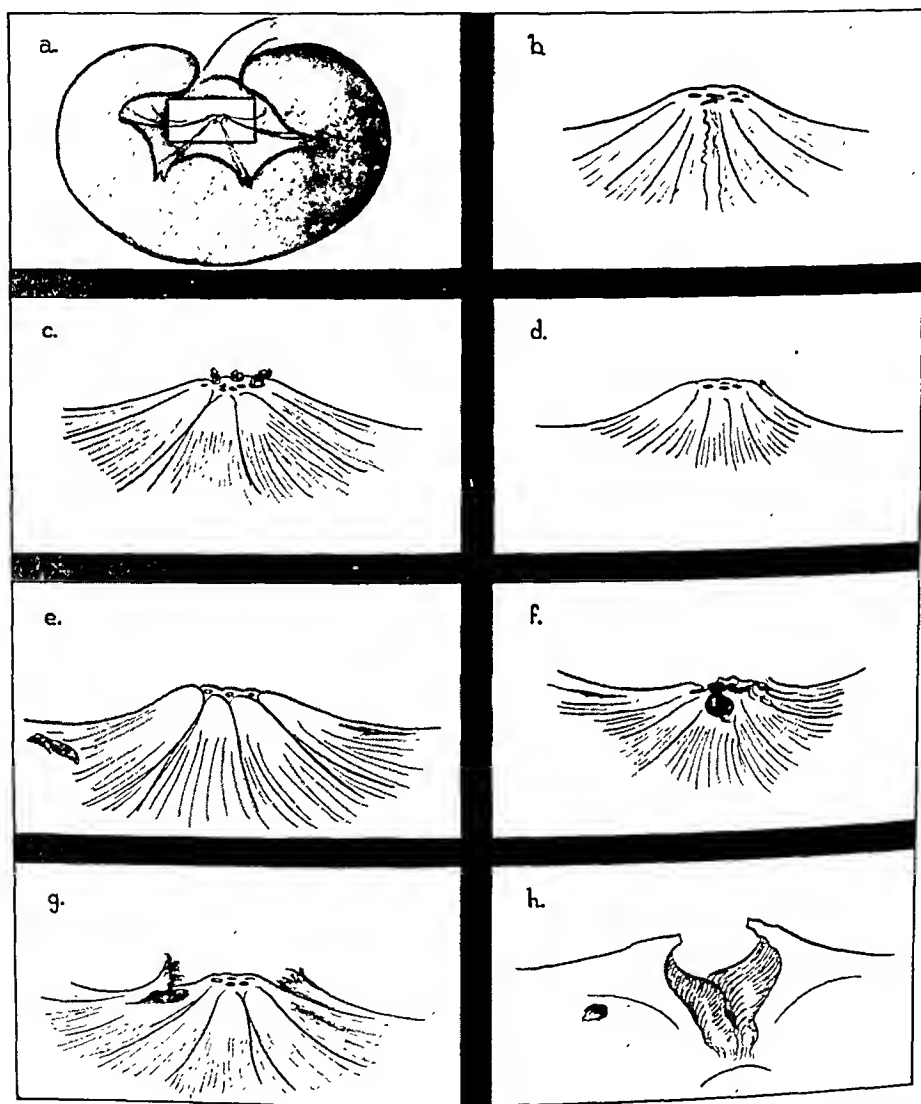
Fig. 11.—Renal papilla in a case of hydronephrosis. Drawing *a* denotes the area depicted; *b*, the tip of the papilla, showing the mouths of the main collecting ducts; *c*, cellular débris and dye plugging the mouths of three main collecting ducts; *d*, papilla presenting a minute epithelial tear on the right side; *e*, two areas of trauma on either side toward the papillary base; *f*, trauma involving the mouths of the duct; *g*, tears with retraction on the lateral aspects; *h*, gross splitting of the papilla.

base was reached the usual small, almost pear-shaped cell constituted the epithelium, in continuity with that of the rest of the pelvic cavity (fig. 15).
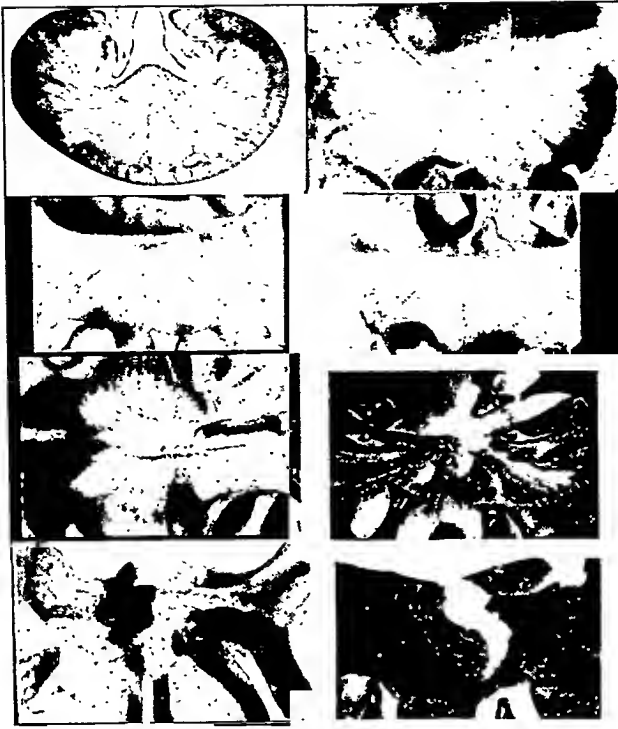
Fig. 12.—Renal papilla in a case of hydronephrosis. The same specimens similarly arranged, which are diagrammatically shown in figure 11.

Fig. 13.—Photomicrograph of the tip of the renal papilla (frozen section). Dilatation of the mouths of a main collecting duct, consequent on hydronephrosis, is evident, and the columnar cells (a) which have absorbed dye present radial striation.

Longitudinal sections of the papilla revealed that these peg-shaped cells were present in the walls of the main collecting ducts and were interspersed with cells of the cuboidal type (fig. 14 *A*). As the cuboidal cells remained clear, the deeply stained peg-shaped cells showed up in marked contrast. They extended from the lumen of the duct and narrowed down as they reached the basement membrane. Many of them showed a definite narrow band of deeper staining at the wider, free end, which abutted on the lumen of the duct. The nuclei were mainly central or toward the lumen. In some respects these cells resembled the columnar cells of the intestine. The number of such readily stained cells became less as the base of the pyramid was reached. Their presence in the otherwise clear collecting ducts gave a ladder-like appearance
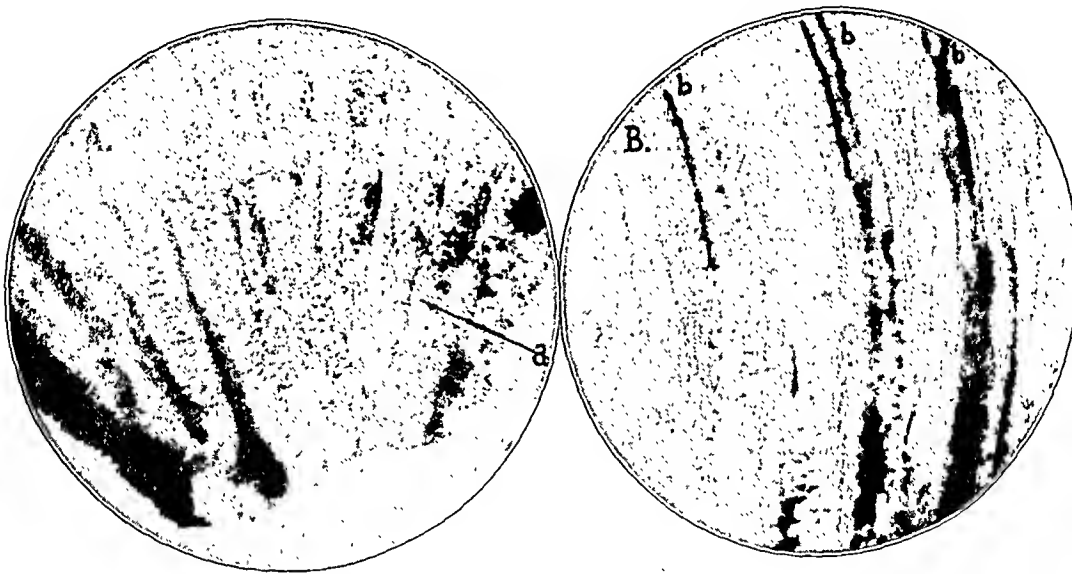
Fig. 14.—Collecting duct system (photomicrographs of frozen sections). *A*, columnar cells (*a*) which have absorbed dye, interspersed with clear cuboidal cells lining the main collecting ducts at the renal papilla. *B*, the collecting duct system toward the base of the papilla. The finer subdivisions of the collecting ducts in this region show absorption of dye by cells of a smaller, more rounded type (*b*).

in longitudinal section (fig. 15 *g*). In ordinary stained paraffin section the cells were somewhat pear shaped, with nuclei usually definitely nearer the lumen of the duct than the basally situated nuclei of the cuboidal cells. It was noted that in the areas where these columnar or peg-shaped cells had taken up a marked degree of staining the immediate underlying tissue also showed appreciable absorption of dye. The underlying tissues of the papilla showed deep staining in instances in which tears had occurred in the overlying epithelial layer or in which there had been direct splitting of the papilla itself.

From near the base of the medulla the subdivisions of the collecting ducts showed a transition from the columnar form of cell to a small rounded type which is characteristic of the ducts from this level outward to their ultimate subdivisions in the cortex (fig. 14 *B*).
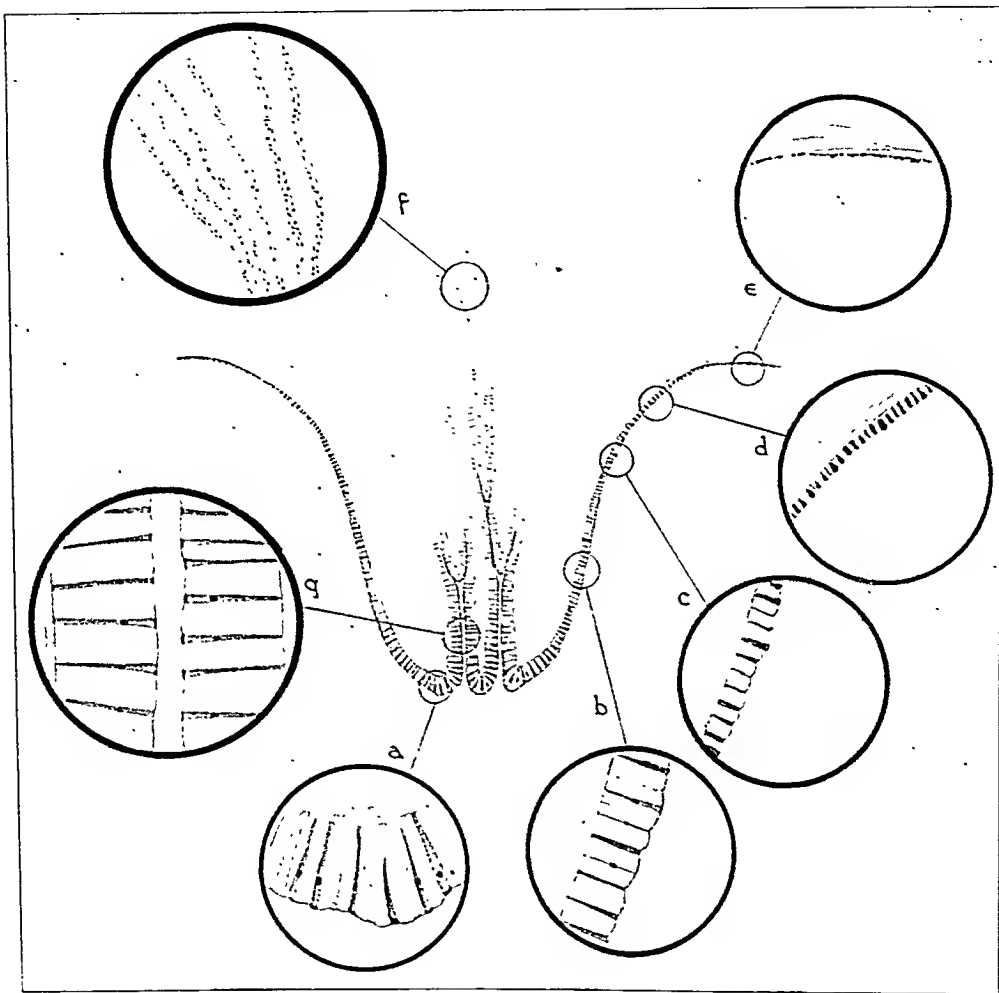
Fig. 15.—Semidiagrammatic representation of the renal papilla (rabbit) in longitudinal section. The covering epithelium of the papilla and the lining of the duct are shown after vital staining. The types of individual cells which absorb dye are depicted by a series of enlarged fields from sites indicated as follows: *a*, tip of the papilla; *b*, *c* and *d*, graded epithelium of the lateral walls; *c*, angle of reflection (these cells will be seen to be similar to those of the pelvic lining); *g*, main collecting duct; *f*, lesser collecting ducts at the papillary base.

Although during life the lymphatics of the renal pedicle were kept under constant observation, no obvious evidence of transmission of dye was noted in these experiments. It may be that lymphatic drainage from these areas is relatively slow. The possibility has been cited of an intrarenal lymphatic system which drains directly into the renal veins, as distinct from an extrarenal or superficial system which drains into the large vessels accompanying the renal pedicle. Confirmation of this is needed.

CONCLUSIONS

1. There is rapid absorption from a totally obstructed hydronephrotic sac into the general circulation of such agents as uroselectan B (known in the United States as neo-iopax) and phenolsulfonphthalein. Indigo carmine is similarly eliminated, but more slowly. Interruption of the lymphatic vessels at the renal pedicle produces no appreciable effect on the rate of absorption; an exclusively venous route, therefore, seems indicated.

2. Rapid lymphatic absorption follows intertubular injection of dyes into the superficial aspects of the cortex. Studies of the ureter and the renal pelvis suggested that absorption from the walls and lumen is relatively slow.

3. Tubular absorption of dyes from the pelvis is usually manifest in about thirty minutes but can occur more rapidly with total obstruction of four to five days. With longer periods of obstruction an hour or more may elapse before dye is evident at the cortex.

4. Suggestive evidence was obtained in several instances of obstruction of five to eight days' standing that the varying pelvic pressure occasioned by peristaltic movements is transmitted directly by fluid continuity from the pelvis to the distal convoluted tubules in the superficial zones of the cortex.

5. Studies of the lining epithelium of the ureter and the renal pelvis were made after vital staining, and the types and reactions of the cells were noted. A selective action with regard to immediate absorption is suggested. Certain cells distributed over the renal papilla as well as in the main collecting ducts are of a columnar type, resembling those of the gastrointestinal tract.

ABSTRACT OF DISCUSSION

Dr. Frank Hinman (San Francisco): Knowing the skill and the meticulous care with which Dr. Morison works, I am sure there can be no question of the accuracy of his observations. When it comes to their interpretation, however, I think there is room for a difference of opinion.

Vital and intravital stains have been a bone of contention from the time they were first used, and whether staining by these methods means contact stain, phagocytosis, cellular secretion or cellular absorption is usually open to question.

So true is this that the most recent book on the physiology of the kidney (Smith, H. W.: The Physiology of the Kidney, London, Oxford University Press, 1937) dismissed the finding of vital stains in one paragraph, stating that the interpretations are so various and uncertain as to prove nothing with respect to the physiology of the kidney.

Now this has nothing particularly to do with the original work of Dr. Morison. He has shown excellent sections of the pelvis and of the collecting tubules, but I think that the question whether his demonstration establishes a route of absorption or the tidal flow in hydronephrosis is open to discussion.

Let me review briefly some of the points against cellular reabsorption as a factor of moment in the explanation of the phenomenon of hydronephrosis.

Hydronephrosis with complete ureteral obstruction is unique. Complete obstruction of the ducts of other glands brings about primary atrophy, whereas only exceptionally, in a few experimental animals does primary atrophy follow complete obstruction of the ureter.

The active portions of the renal tubule are the glomerulus, the proximal convolution, the loop of Henle and the distal convolution. The remaining parts of the system are purely conductive and have no more to do with the formation and secretion of urine than does the renal pelvis, the ureter or the bladder.

When the ureter is obstructed there is at once a back pressure on the secreting and conducting parts of the tubule, and this increases until it equals secretory pressure; nevertheless, the formation of urine continues, with dilatation and progressive atrophy of the secreting portions of the tubules, until at the end of the process only the glomerulus and a straight tube remain.

A section of a hydronephrotic sac after intravital staining shows that the convoluted tubular area takes up the stain, thus presumably demonstrating vital activity of the cells lining the tubules. This activity is thought to be secretory. Absorption occurs mostly in the loop of Henle and in the distal convolution. Physiologists now speak of the clearance of substances; for example, the clearance of uric acid, of chloride, of creatinine and of other substances. The concentration of any such substance in the urine multiplied by the amount of urine formed in the unit of time, divided by its concentration in the blood, measures its clearance during this period. To what extent the clearance of any particular substance is affected by filtration, secretion and absorption has not been fully determined, though the fact that these three processes occur has been fully established.

The final stage of hydronephrosis, with complete obstruction of the ureter after the process of group destruction and group preservation, has been demonstrated by Dr. C. M. Johnson. The tubules were dissected out under the microscope after maceration from an arterial injection of hydrochloric acid. All of the active secretory portions of the tubular system had disappeared, and only the glomerulus, with a relatively short conducting tube, was left; yet the glomerulus still filtered a certain amount of urine, keeping up the pressure in the sac, which continued to enlarge slowly until even the glomerulus had become atrophied. This marks the stage of complete hydronephrotic atrophy.

An experiment carried out in conjunction with Dr. Carroll has its significance in reference to the role of absorption in hydronephrosis. Ligatures were so placed as to obstruct the collecting ducts of the papilla in the kidney of the rabbit without obstructing the ureter and so placed also that the circulation of the kidney was in no way hampered. Only the collecting ducts, which carry the urine from the secreting portion to the pelvis of the kidney, were obstructed. A series of sections made seven, forty-two, eighty-four and one hundred and eighty days thereafter showed the results, and each was compared with a hydronephrotic specimen

taken after a similar period of ureteral obstruction. Atrophy of the substance of the kidney following obstruction of the duct resembles primary atrophy more than hydronephrotic atrophy. In the experiment referred to, at eighty days almost all secreting elements had completely disappeared. Atrophy is much more rapid than after ureteral obstruction.

As a final argument against cellular activity as a route of reabsorption, it is known that in the presence of hydronephrosis there must be not a selective but a gross back flow or absorption from the renal pelvis, if for no other reason than that the content of the sac at any stage of hydronephrosis is similar in composition to that which the kidney would secrete at the time if the obstruction were removed, provided the kidney were still capable of secretion.

It is also known from studies on back flow (whether pyelovenous, pyelolymphatic, pyelotubular, tubulovenous, tubulolymphatic or interstitial) that the pressure required to produce this back flow diminishes as the period of ureteral obstruction lengthens. It is known, too, that intrapelvic pressure falls with the duration of hydronephrosis. These two facts seem to agree.

Lymphatic back flow explains satisfactorily the condition of chyluria. The chyle which cannot find normal exit by the thoracic duct flows back into the pelvis of the kidney, and this lymphatic communication with the pelvis can often be demonstrated pyelographically. If chyle can flow back from lymphatics into the pelvis after obstruction of the lymphatics, it seems reasonable to suppose that the urine in the pelvis can flow into these lymphatics after obstruction of the ureter.

Cellular activity of the tubules would seem to perform only a minor and unessential part in the pathogenesis of hydronephrosis.

The pictures Dr. Morison has shown provide an excellent demonstration of the collecting system.

Dr. Charles P. Mathé (San Francisco): It has been a great pleasure to hear Dr. Morison describe his splendid experimental study on the routes of absorption of dyes in the presence of hydronephrosis with total obstruction of the ureter. Experiments on various phenomena occurring in association with hydronephrosis were initiated some years ago, when Dr. Morison was a member of the urologic staff of the University of California Medical School. As a former staff confrère, I wish to felicitate him on the splendid work that he has continued and has since accomplished in this field.

His findings are significant. In experimenting with the dyes commonly used for studying renal function he observed that uroselectan B and phenolsulfonphthalein are rapidly absorbed by the general circulation when injected into a totally obstructed hydronephrotic sac, whereas indigo carmine similarly injected is eliminated much more slowly. Why should there be such a variance in the rate of absorption of phenolsulfonphthalein and of indigo carmine? In functional studies of the normal kidney, indigo carmine is usually observed to appear in three to five minutes after intravenous injection. The fact that interruption of lymphatic drainage had no influence on the rate of absorption shows that the lymphatics play a minor role in the absorption of dyes. Dr. Morison's observations on tubular absorption are interesting.

His experiments have cleared up the controversial subject of pyelovenous back flow. He has proved that such back flow is not normal but occurs only when trauma caused by overdistention of the pelvis forces injected material into the general circulation.

The clinical significance of the facts obtained by this series of experiments is important. In the presence of a closed, infected hydronephrotic lesion of the kidney, absorption of toxins resulting from bacterial invasion probably occurs in

the same manner as does absorption of dye. This explains the tremendous relief obtained by preliminary nephrostomy in the two stage surgical removal of a kidney involved in a closed pyohydronephrotic lesion.

Dr. Morison's experiments also point out the value of measuring pelvic capacity in order to determine the amount of an opaque medium that should be injected for the purpose of making retrograde pyelographic studies and the quantity of an antiseptic solution which should be utilized in carrying out pelvic lavage, because overdistention has been definitely shown to produce injury.

Dr. Morison's experimental work will prove to be of great clinical significance.

Dr. Duncan M. Morison (Edinburgh, Scotland) : For those who are not particularly interested in experimental work and prefer clinical data, a histophysiologic presentation tends to be tedious.

My paper was put forward purely as an interim report on the work which my associates and I are pursuing. We hope in time, by using such mediums as dyes, to trace the routes by which infection is probably carried from the walls and lumen of the upper portion of the urinary tract to the general system. Much yet remains to be done, and I should be grateful if at any time when any one has ideas on the subject he would communicate with me.

EFFECT OF EXPERIMENTALLY FORMED TUMORS ON THE MUSCULOSKELETAL SYSTEM OF THE RAT

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AND

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There are many published studies of the development of malignant tumor after the topical application or injection of anthracene derivatives.[1] Only a few of these investigations, however, have dealt with attempts to produce such a tumor in or near a bone or a joint.[2] The present study is devoted to this point and specifically to the effects of such a tumor on skeletal tissue, as noted roentgenographically and histologically. In the course of the experiments several noteworthy complications appeared in addition to the tumors. Routine histologic examination of the latter with the aid of hematoxylin and eosin staining was supplemented by comparative studies made with the Laidlaw silver method [3] and with the so-called fluorescent technic.[4]

METHOD

The activating agent used was 1,2,5,6-dibenzanthracene. Three milligrams of dibenzanthracene was dissolved in 1 cc. of benzene or suspended in 1 cc. of melted lard.[5] Injections were made into 35 adult albino rats each weighing about 150 Gm.[6]

1. Cook, J. W., and Kennaway, E. L.: Chemical Compounds as Carcinogenic Agents, Am. J. Cancer **33**:50 (May) 1938.

2. (a) Lacassagne, A.: Essais de production de cancer chez le lapin au moyen du 1:2:5:6 dibenzanthracène, Compt. rend. Soc. de biol. **114**:660, 1933. (b) Bernard, J.: L'érythro-leucémie expérimentale provoquée par le goudron, Sang **8**:28, 1934. (c) Ilfeld, F. W.: The Experimental Production of Visceral Tumors with Hydrocarbons, Am. J. Cancer **26**:743 (April) 1936. (d) Dunning, W. F.; Curtis, M. R., and Bullock, F. D.: Respective Roles of Heredity and Somatic Mutation in the Origin of Malignancy, ibid. **28**:681 (Dec.) 1936. (e) Brunschwig, A., and Bissel, A. D.: Production of Osteosarcoma in a Mouse by the Intra-Medullary Injection of 1:2 Benzpyrene, Arch. Surg. **36**:53 (Jan.) 1938.

The accompanying table summarizes the procedure and the protocols for these 35 rats, in 16 of which tumor developed.

Macroscopic Findings.—The size of the new growths varied from that of a pea to that of an orange. Most of the tumors were firm and clearly delimited. On section they showed a gray fibrous tissue (fig. 1). A few scattered cysts and some yellowish necrotic areas were also encountered. In most of these, examination with filtered ultraviolet radiation revealed sites of golden fluorescence.

Roentgenographic Findings.—Roentgenographic examination of the rats revealed that most of the tumors, even though they abutted on skeletal tissue, had provoked little or no periostitis. Furthermore, none of the new growths themselves showed any bone formation.

3. Stout, A. P.: Human Cancer, Philadelphia, Lea & Febiger, 1932.

4. Sutro, C. J.: Fluorescent Microscopy, Arch Path. **22**:109 (July) 1936.

5. (*a*) Cook, J. W.; Hieger, I.; Kennaway, E. L., and Mayneord, W. V.: Production of Cancer by Pure Hydrocarbons, Proc. Roy. Soc., London, s.B **111**: 455 (Oct. 1) 1932. (*b*) Andervont. H. B.: Production of Dibenzanthracene Tumors in Pure Strain Mice, Pub. Health Rep. **49**:620 (May 25) 1934.

6. Studies were also made on 19 additional rats, each of which was given 2 cc. of either warm lard or benzene, with or without dibenzanthracene. When dibenzanthracene was given, each cubic centimeter of menstruum contained 5 mg. of the drug. The injections were made into the right axilla, and the animals were killed at intervals ranging from four to two hundred and seventy days afterward. In these animals no tumors developed.

As long as two hundred and seventy days after the injection, filtered ultraviolet radiation sometimes still revealed the fluorescent dibenzanthracene in the cysts found at the site of injection ((*a*) Berenblum, I., and Kendal, L. P.: The Production of Tumors in the Fowl with a Colloidal Solution of 1:2:5:6-Dibenzanthracene, Brit. J. Exper. Path. **15**:366 (Dec.) 1934. (*b*) Lorenz, E., and Shear. M. J.: Studies in Carcinogenesis, Am. J. Cancer **26**:333 (Feb.) 1936. (*c*) Berenblum, I., and Kendal. L. P.: The Destruction of 1:2:5:6 Dibenzanthracene in the Mouse, Biochem. J. **30**:429 (March) 1936. (*d*) Sannie, C.: Carcinogenic Action and Absorption and Fluorescence Spectra of 1:2 Benzpyrene, ibid. **30**:704 (April) 1936. (*e*) Peacock, P. R.: Evidence Regarding the Mechanism of Elimination of 1:2-Benzpyrene, 1:2:5:6-Dibenzanthracene and Anthracene from the Blood Stream of Injected Animals, Brit. J. Exper. Path. **17**:164 (June) 1936. (*f*) Chalmers, J. G., and Peacock, P. R.: Further Evidence Regarding the Elimination of Certain Polycyclic Hydrocarbons from the Animal Body, Biochem. J. **30**:1242 (July) 1936. (*g*) Hieger, I.: On the Mechanism of Carcinogenesis by Chemical Compounds, Am. J. Cancer **28**:522 (Nov.) 1936; (*h*) The Fluorescence Spectrum of 3-4 Benzpyrene, ibid. **29**:705 (April) 1937). It was interesting to note that the granulation tissue examined twenty-five days after the first injection of benzene plus dibenzanthracene contained numerous mitotic cells, some of which were located in the lumens of capillaries.

Results of Injection of Dibenzanthracene in Rats

Group	Number of Rats in Experiment	Number of Rats with Tumor	Site of Injection	Total Number of Injections per Rat and Interval Between Injections	Contents of Each Injection	Duration of Experiment, Months	Site of Tumor	Size of Tumor	Microscopic Examination
A	4	0	Pericranial tissues in occipital region	6 injections (monthly)	3 injections each containing, 1.5 mg. dibenzanthracene in 0.5 cc. of benzene; 3 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of melted lard	8	No tumor		
B	3	2	Pericranial tissues in occipital region	6 injections (monthly)	3 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of benzene; 3 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of melted lard	7 and 15	Occiput	Pea and plum size	Cellular fibrosarcoma
C	4	0	Pericranial tissues in occipital region	4 injections (monthly)	2 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of benzene; 2 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of melted lard	8	No tumor		
D	4	3	Parosteal tissues of middle third of femur	5 injections (monthly)	3 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of benzene; 2 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of melted lard	8 and 10	Thigh, knee and leg	Plum size	Cellular fibrosarcoma
E	6	5	Lower lumbar vertebrae (spinous process)	6 injections (bimonthly)	1 injection of 1.5 mg. dibenzanthracene in 0.5 cc. of benzene; 4 injections each containing 1.5 mg. dibenzanthracene in 0.5 cc. of melted lard; 1 injection of 6 mg. of dibenzanthracene in 2 cc. of melted lard	12 to 14	Lumbar vertebrae region	Lemon size	Mixed cellular sarcoma
F	6	2	Region of knee joint	3 injections (bimonthly)	First injection, 1.5 mg. of dibenzanthracene in 0.5 cc. of benzene; second injection, 3 mg. of dibenzanthracene in 1 cc. of melted lard; third injection, 6 mg. of dibenzanthracene in 2 cc. of melted lard	15 and 19	Thigh, knee and leg	Plum size	Cellular fibrosarcoma
G	4	2	Major marrow cavity of tibia (surgical procedure)	One implantation	1.5 mg. dibenzanthracene in 0.5 cc. of melted lard	19 and 23	Thigh, leg and knee	Cherry and orange size	Cellular fibrosarcoma; in another, carcinoma in tibia secondary to primary intestinal carcinoma
H	4	2	Dorsal aspect of scapula	1 injection	6 mg. of dibenzanthracene in 2 cc. of lard	8 and 10	Axilla, ribs, lungs and humerus	Cherry to plum size	Cellular fibrosarcoma

Indeed, in some of the animals they were found to have eroded parts of the calvarium, the knee joints, the femurs, the tibias, the humeri, the laminas of the lumbar vertebrae and the ribs (fig. 2).

Microscopic Findings.—Histologic study revealed that most of the tumors were cellular fibrosarcomas. Some resembled rhabdomyosarcoma or myxosarcoma, and others somewhat resembled liposarcoma.

The cell nuclei of the new growths were of various shapes and types. Some were round, vesicular or flat. Others were multinuclear, and still
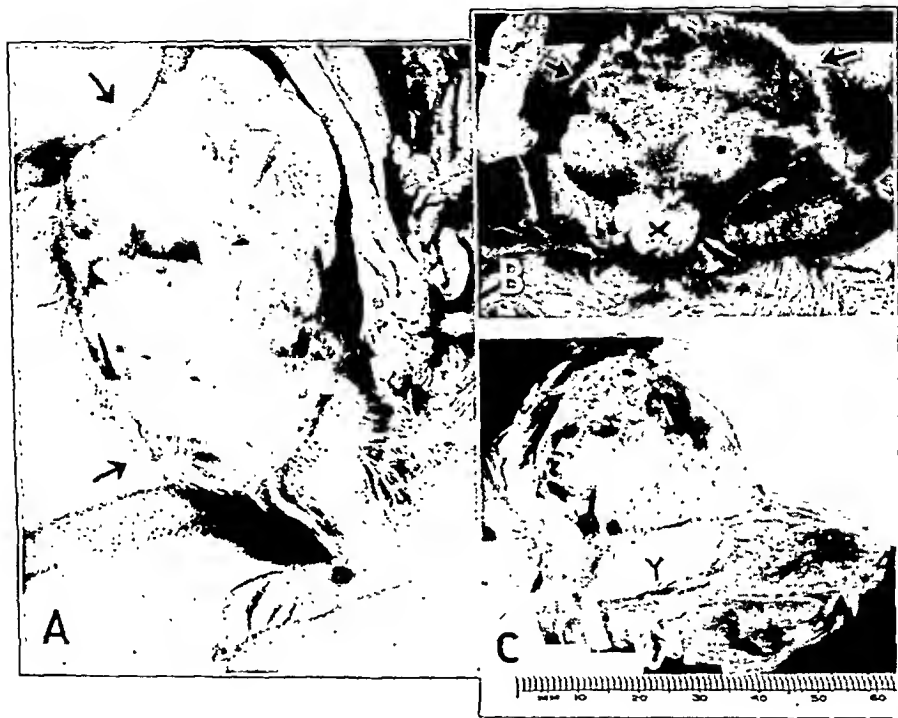
Fig. 1.—*A*, photograph of a rat (group D) with a sarcoma of the right thigh, knee and leg. The tumor has been bisected. *B*, photograph of another rat with a solid sarcoma about the right knee, leg and thigh. Note the cyst (*X*) in the right groin; it contained lardaceous material. *C*, photograph of the bisected head of a rat (group B) showing a fibrosarcoma on the calvarium. *Y* indicates the brain. Note the areas of hemorrhage in the tumor.

others resembled in certain respects the nuclei of bone marrow cells. Apparently the invading tumors had incorporated and activated the contiguous soft tissues and had thus induced the formation of sarcomas of the mixed cell type. In no case, however, was there any evidence of an osteogenic tumor (fig. 3).
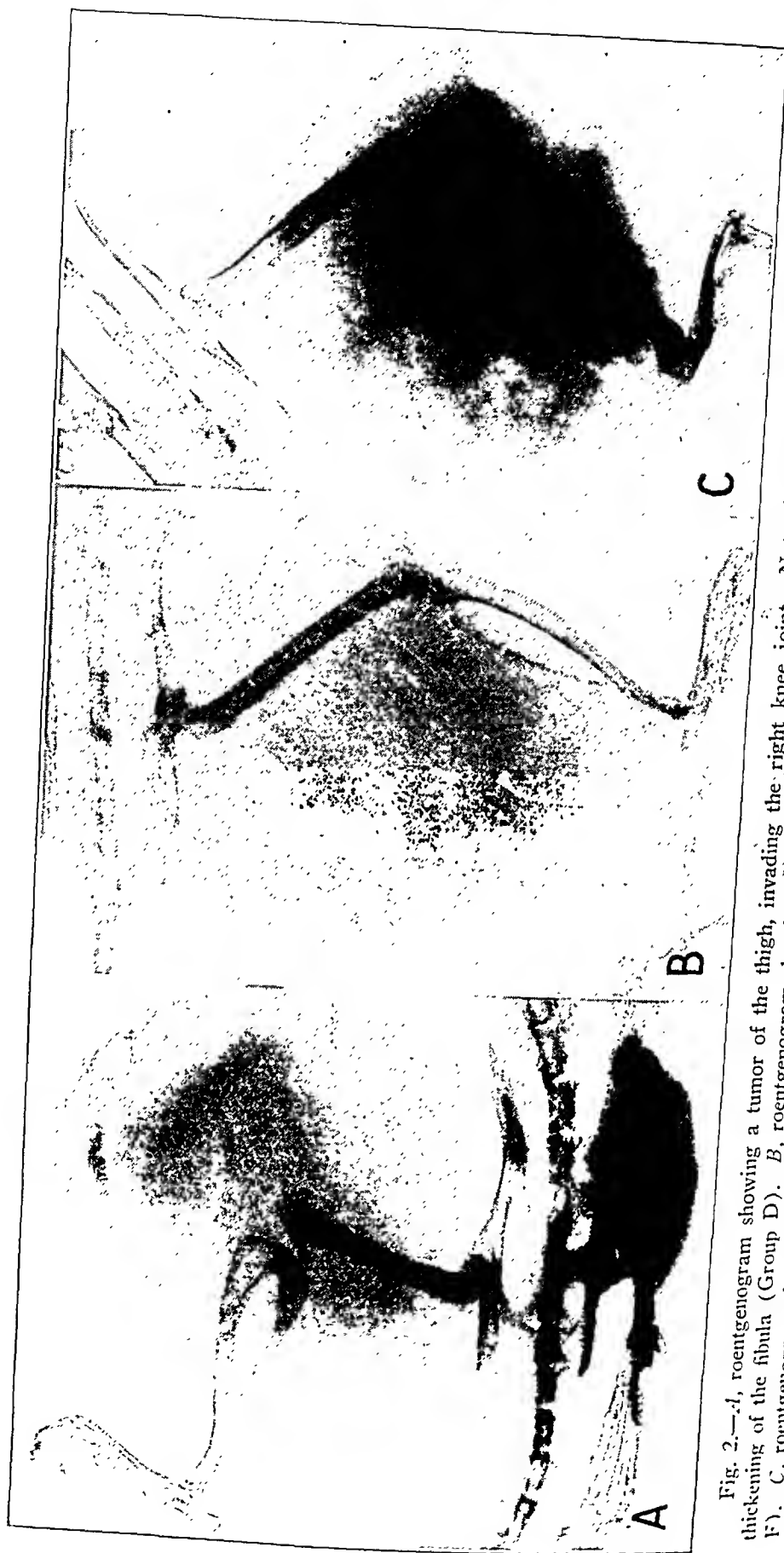
Fig. 2.—A, roentgenogram showing a tumor of the thigh, invading the right knee joint. Note the thickening of the fibula (Group D). B, roentgenogram showing a large tumor encasing the thigh and leg. C, roentgenogram showing a large tumor invading the tibia, knee and femur. Note the widening of the interosseous space and the tibia (Group G). Note the absence of periostitis (Group F). Dibenzanthracene was introduced into the marrow cavity of
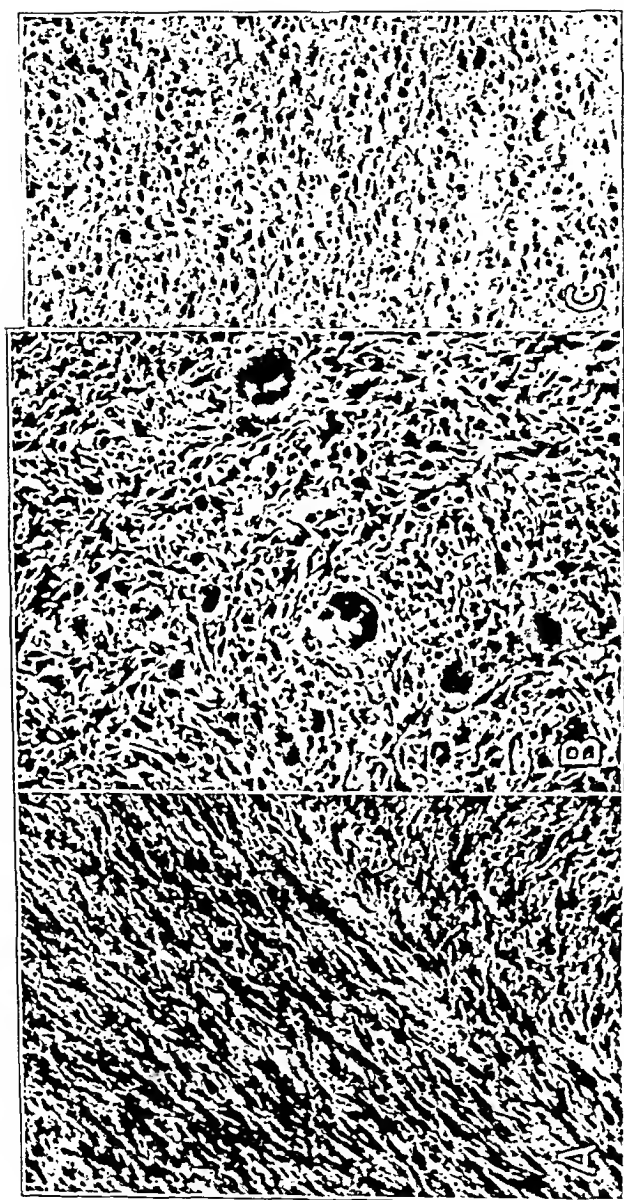
Fig. 3.—*A*, photomicrograph showing an area of fibrosarcoma. *B*, photomicrograph showing the large giant cells of a tumor. *C*, photomicrograph showing an area of immature tumor cells.

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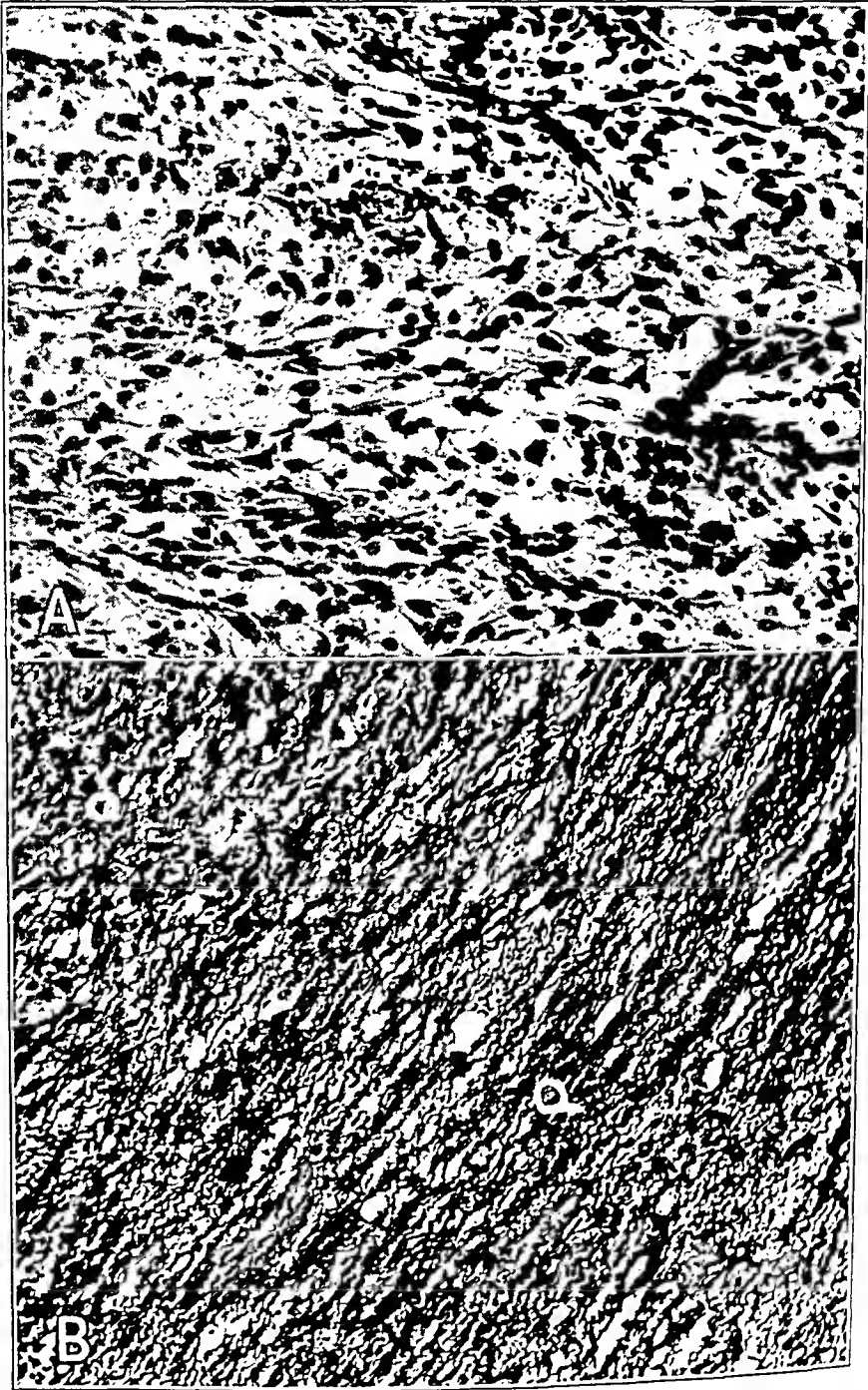
Fig. 4.—*A*, photomicrograph demonstrating an area of myxoma-like cells in the sarcoma. *B*, photomicrograph showing the Laidlaw silver reaction in the tumor. Note in the area marked *O* that the cells are positive and the fibrils are relatively sparse. In the area marked *a* the fibrils are closely set and numerous, but the nuclei do not stain.

Fig. 5.—*A*, photomicrograph revealing an area of necrosis in the tumor (stained with hematoxylin and eosin). *B*, photomicrograph of the same area of necrosis reveals clearly the fibrils (stained with Laidlaw silver reagents).
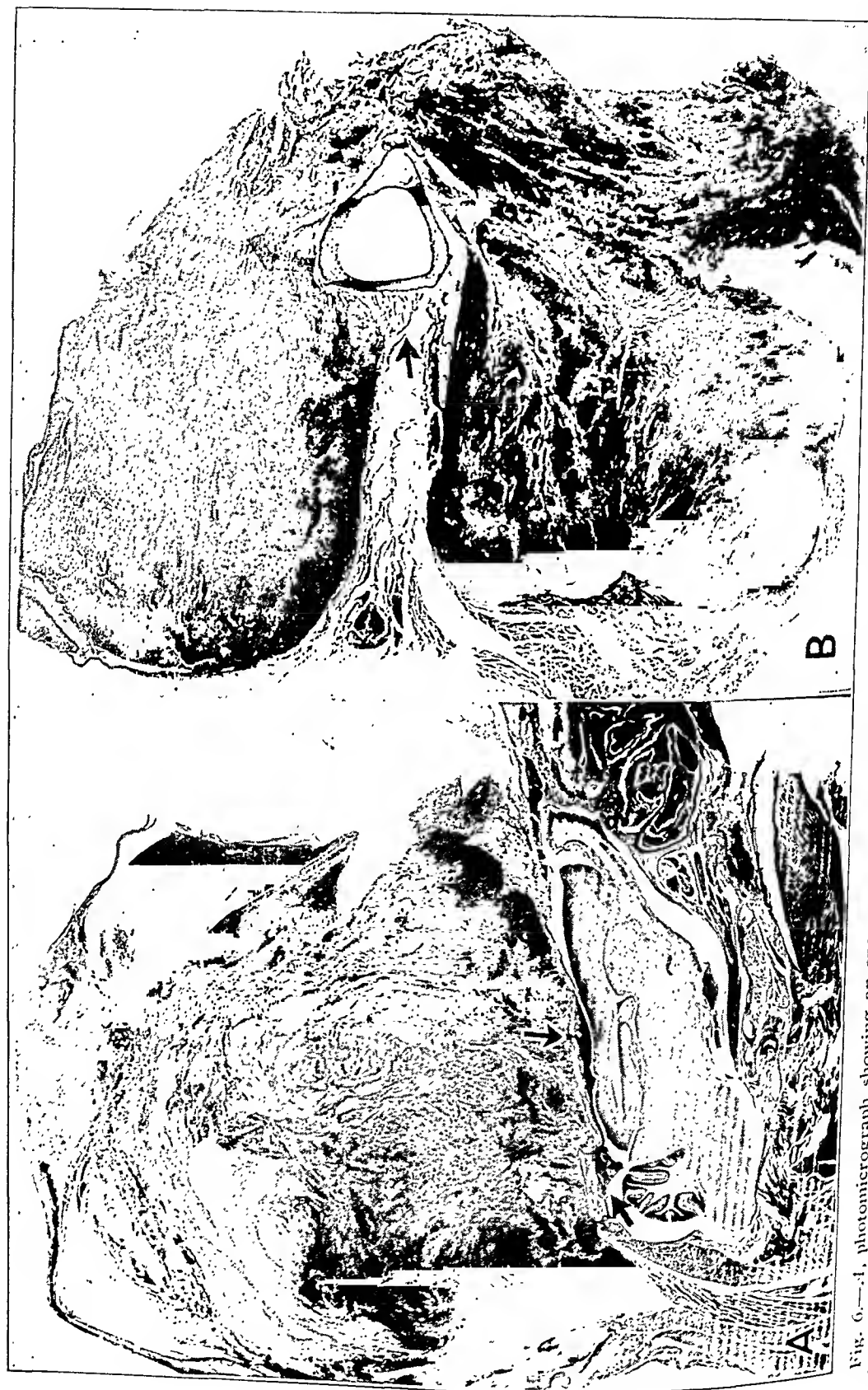
Fig. 6.—A, photomicrograph showing an enormous tumor situated on the calvarium. It is invading the cranial cavity via a small perforation in the calvarium (arrows). B, photomicrograph of a fibrosarcoma of the femur. Periostitis is present only where the tumor does not touch the cortex (arrow).

Fig. 7.—A, photomicrograph revealing that the tumor has entered the quadriceps pouch of the knee joint. The posterior capsule is also being invaded by tumor (fig. 1 A). B, photomicrograph showing fibrous ankylosis of the knee, secondary to invasion of the capsule by tumor tissue (arrow). F, the femur; T, the tibia.

Fig. 8.—Photomicrograph showing the fibrosarcoma entirely replacing the bones in the knee joint. It spared only the distal epiphysial plate of the femur (arrow). Compare with figure 2 C.
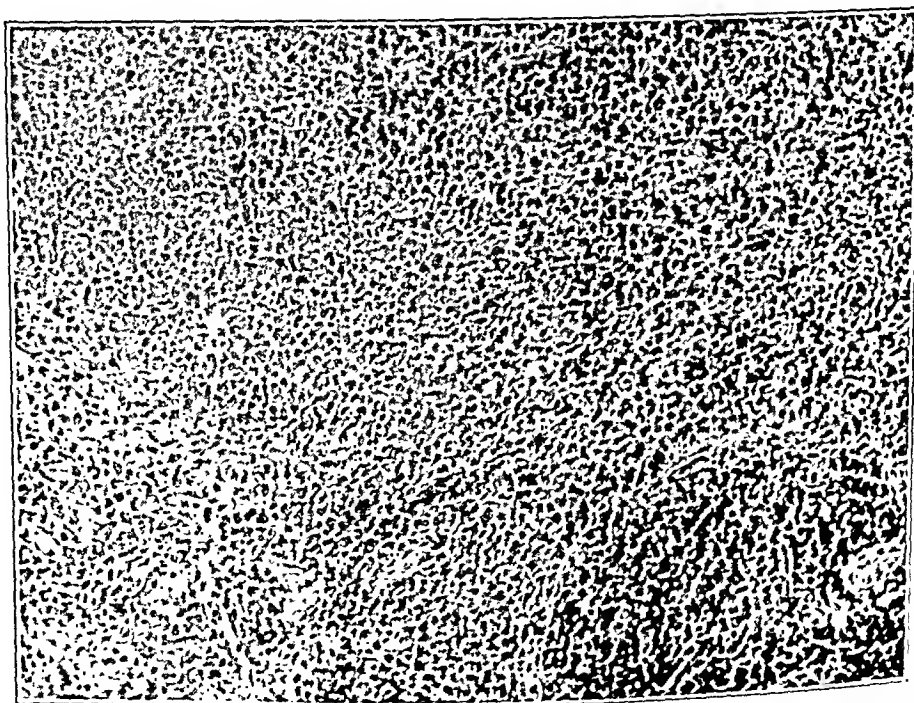
Fig. 9.—Photomicrograph showing a definite reticulum cell hyperplasia in the spleen of a rat sixty-eight days after the subcutaneous injection of 2 cc. of dibenzanthracene in lard.

When the Laidlaw silver reagents were used in histologic examination of the tumors, many of the tumor cells (especially those of the multinucleated type and also some of those in the myxomatous areas) proved to be "silver positive." The intercellular material of the tumors usually showed few fibrils. It was interesting to note, however, that in certain areas where early necrosis was in evidence and where the hematoxylin and eosin stains failed to bring out clearly the outlines of the cells and the fibrils of the matrix, the Laidlaw silver reagents revealed these plainly, occasionally also revealing the nuclei of the cells (figs. 4 and 5).

It may be assumed that those cells which showed positive staining in response to the presence of Laidlaw reagents represented still undifferentiated mesenchyme and were similar to bone marrow cells in their manner of reaction.[7]

The amount of periosteal reaction revealed by histologic examination of the skeletal tissues was minimal. Even when the tumor lay against the outer lamelli of the cortex, new bone formation was not a salient feature. However, in some cases the sarcoma did invade the contiguous bone and joints to some extent. In 1 animal the tumor invaded the posterior capsule of the knee, penetrating into the articular cartilage and inducing slight proliferation of the new bone on the tendon surface of the patella. In another rat the tumor attached itself to the para-articular surface of the knee capsule. The knee joint underwent fibrous ankylosis (figs. 6 and 7).

Intra-articular injection of dibenzanthracene resulted in the development of a sarcoma which invaded most of the structures of the knee joint and partially replaced the crucial ligaments, the semilunar cartilages and the synovial linings. In addition, the tumor extended into the marrow cavity at the distal end of the femur.

Even the implantation of dibenzanthracene by surgical means into the marrow of the tibia did not produce an osteogenic tumor. It did, however, produce in 1 rat an invasive tumor which destroyed the entire lower end of the femur with the exception of its distal epiphysial plate (fig. 8). In another rat of this group a metastatic carcinoma was found in the tibia, just at the site of implantation of the anthracene. The primary tumor in this case was in the intestine.

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7. Laidlaw stated that cellular elements derived from the entoderm and ectoderm as well as those from hemopoietic, lymphatic and reticuloendothelial cells are "black-positive" in their staining reaction, while all other elements are "black-negative."

This was the only case in the entire series in which there was evidence of metastasis. On the other hand, most of the spleens, especially those of the tumor-bearing rats, showed definite hyperplasia of reticulum cells (fig. 9). The hemopoietic cells were also hyperplastic.

When examined with the aid of fluorescent microscopic technic many of the tumors revealed golden yellowish areas, usually in or near the cysts. This was not a constant finding, however, especially in rats which had had tumors for longer than twelve months after the initial

Fig. 10.—Large retroperitoneal sarcoma which encased the vertebral column (group E).

injection. Organs of the tumor-bearing rats and those without tumors were examined in the same way as the growths themselves, but no fluorescent areas were found.

COMPLICATIONS

Para-articular Ossification.—In 5 rats the injection of dibenzanthracene into the region of the lower lumbar vertebrae resulted in a large tumor. While the tumor did infiltrate the bony laminas (figs. 10

Fig. 11.—*A*, photomicrograph of another tumor in the same group, showing the relative location of the mass with reference to the vertebral column. The arrow points to the body of the lumbar vertebra. *B*, photomicrograph of the same tumor at another level, showing invasion into the lamina (arrow).

Fig. 12.—*A*, roentgenogram of tumor of the soft tissues in the lumbar portion of the vertebral column. Note the fracture and nonunion of the right tibia as well as the para-articular ossifications in the region of the right ankle. Periostitis and loss of some of the digits are also present. Spontaneous amputation above the ankle joint is noted in the opposite limb. *B*, enlargement of the roentgenogram of the right leg (fig. 12 *A*), revealing clearly the periostitis of the tibia and of the metatarsal bone. Note the para-articular ossifications.
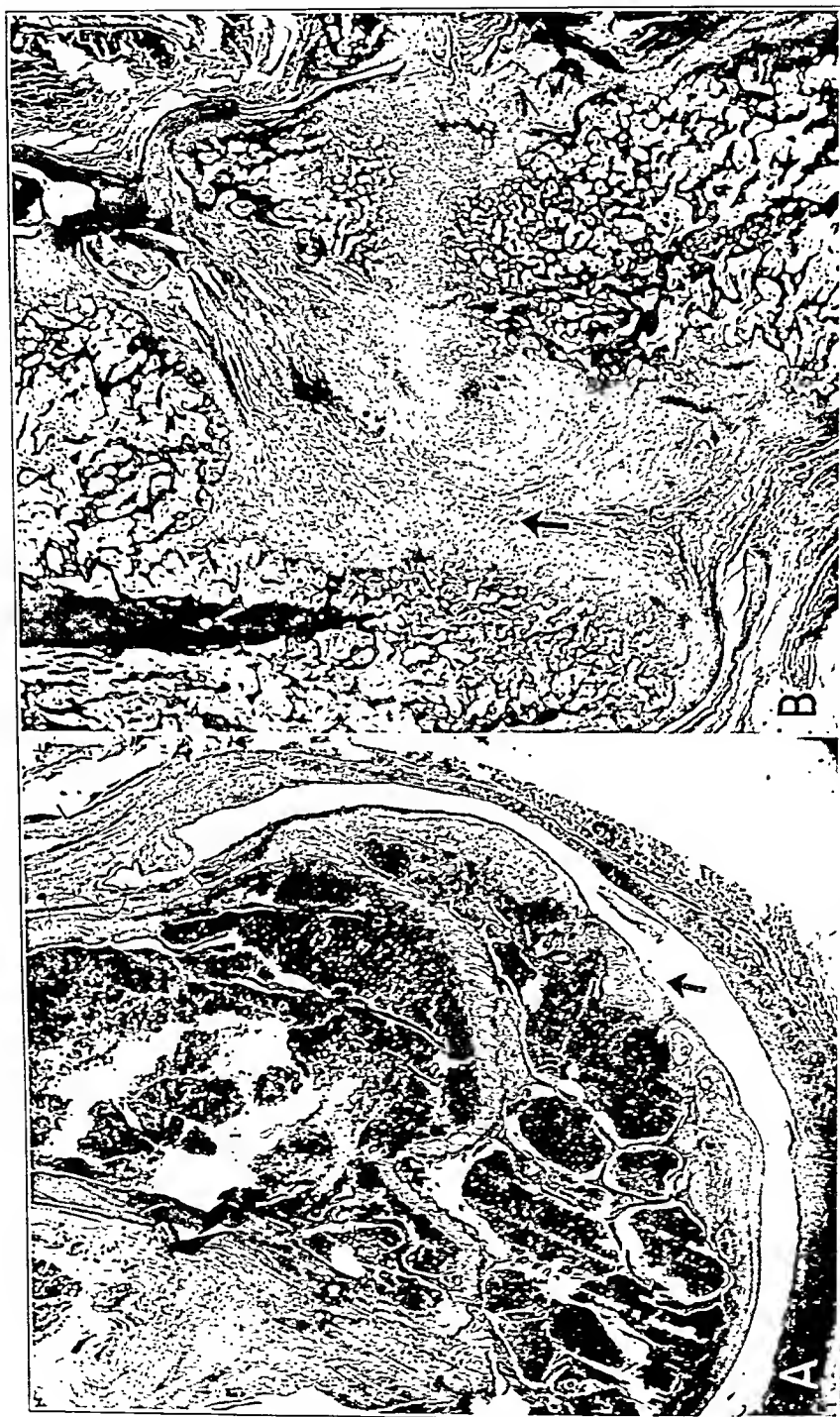
Fig. 13.—A, photomicrograph of the articular end of the left femur (same side as stump in figure 12 A), revealing definite arthritic manifestations, probably of neurotrophic origin. B, photomicrograph showing fibrous union of the fractured tibia in another rat in group E.

and 11), there was no case in which it invaded the spinal cord. The tumor-bearing animals showed gradually increasing paresis of the lower limbs. In 1 tumor-bearing rat the roentgenogram showed absence of several toes on the right foot, evidences of periostitis in one of the metatarsal bones and several para-articular ossifications in the region of the right ankle joint (figs. 12 and 13). Furthermore, it could be noted that the fracture of the right tibia had failed to unite. The other leg revealed a healed stump above the ankle, subsequent to a spontaneous amputation. The left knee joint showed definite arthritic
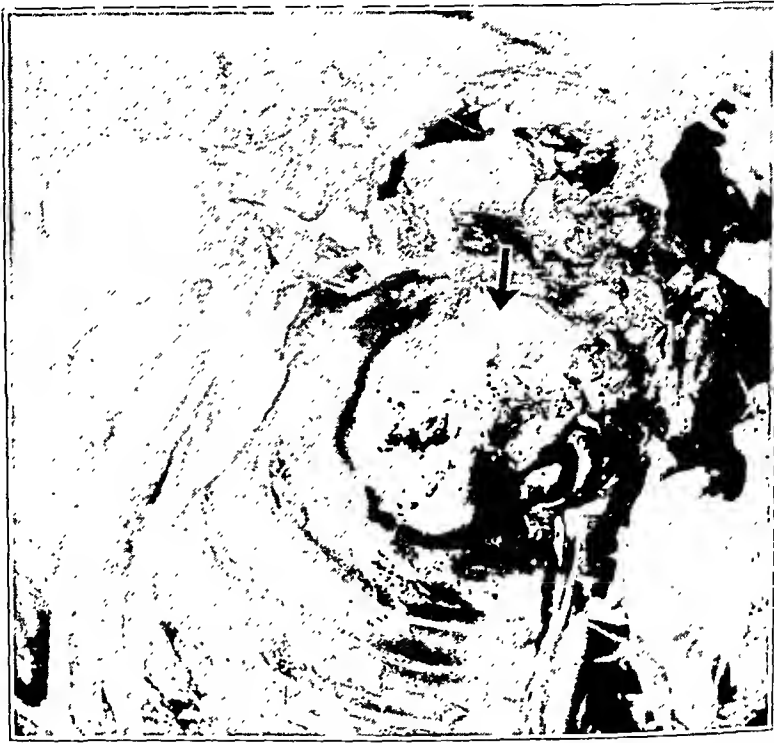
Fig. 14.—Photograph of a sarcoma invading the wall of the chest (arrow).

changes on microscopic examination. In another animal also, with a tumor in the lower vertebral column, nonunion of a fractured tibia was noted. These findings strongly suggest that the tumor produced a neurotrophic disturbance with secondary skeletal changes, analogous with that found clinically in cases of tabes dorsalis or transverse myelitis.[8]

Hypertrophic Periosteal Osteophytosis.—In another series of rats, in which dibenzanthracene was injected into the posterior aspect of the right scapula, 1 rat had a tumor about as large as a plum. The mass extended across the axilla and was attached to the humerus, the ribs

8. Corbin, K. B.: Alterations in the Hip Joint After Deafferentation, Arch. Surg. 35:1145 (Dec.) 1937.

and the lungs (fig. 14). On histologic examination the cortex of the femur as well as that of the phalanges of the toes revealed evidence of definite increase in the number of outer lamellas, as shown by the cement lines. This is interesting as a possible indication of early hypertrophic periosteal osteophytosis. Further work along these lines is being done.[9]

SUMMARY

In this study, experimentally induced sarcoma, even when growing in tissues contiguous to skeletal parts, did not show any strong tendency to invade the skeleton. Even when a tumor was produced in the skeleton it was not an osteogenic sarcoma. (It should be noted, however, that 1 instance has been reported in which an osteogenic sarcoma was induced by dibenzanthracene.[2]) When invasion into the skeletal system occurred, it was by way of the capsule, as in relation to the knee joint: sometimes by way of the sutures, in relation to the calvarium, and less commonly by direct resorption of the cortex. Even when encased by an enormous tumor, however, the contiguous bone showed strikingly little periosteal reaction to the growth.

The presence of tumor in the vicinity of the spinal cord resulted in the formation of para-articular ossifications and skeletal abnormalities, which were interesting in that they simulated roentgenographically those sometimes noted in connection with neurotrophic disturbances in man.

In general, histologic examination of the tumors frequently showed it to be a mixed tumor containing elements to be found in fibrosarcoma, rhabdomyosarcoma and liposarcoma. In some of the neoplasms there were areas in which the tissue bore a striking resemblance to that of myxoma. When the Laidlaw silver stain was used, some of the nuclei in these areas, as well as nuclei apparently of the primitive types, stained "positive," and as a rule there was a concomitant sparsity of fibrils about such nuclei.

In both macroscopic and microscopic examination of the tumors and organs, filtered ultraviolet radiation was used to help establish qualitatively the presence or absence of the fluorescent drug dibenzanthracene. However, no residue of the drug could be detected in any of the organs, although it was revealed in the growths.

9. Compere, E. L.; Adams, W. E., and Compere, C. L.: Generalized Hypertrophic Pulmonary Osteo-Arthropathy, Surg., Gynec. & Obst. **61**:312 (Sept.) 1935.

SIXTY-EIGHTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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MISCELLANEOUS

Roentgen Therapy in Acute Osteoporosis.—Osteoporosis is defined by Mumford [34] as that condition of bone which follows demineralization or absorption of the mineral salts of the bone. It is demonstrated by a thinning of the bone shadow in the roentgenogram. The author feels that osteoporosis should be classified as symptomatic or asymptomatic. The type with symptoms (the acute bone atrophy of Sudeck) responded to roentgen therapy in 5 of 6 cases. Roentgen therapy is administered in such dosage that erythema and burns will not occur.

Peritendinitis Calcarea.—Sandstrom [35] reports the results of roentgen treatment of calcaneous deposits in tendons, muscle and connective tissue in 329 cases. The deposits were located in the neighborhood of the shoulder, elbow, hip and knee joints, wrist, fingers and toes. He also reports on pathologic specimens obtained in 13 cases. In a number of conditions which are commonly classified as subdeltoid bursitis satisfactory therapeutic results were obtained with roentgen treatment.

Orthostatic Albuminuria.—According to Becher,[36] orthostatic albuminuria is best called lordotic albuminuria, because lordosis is the cause of the lesion. Investigations by Jekle have indicated that lordosis leads

34. Mumford, E. B.: J. Bone & Joint Surg. **20**:949, 1938.

35. Sandstrom, C.: Am. J. Roentgenol. **40**:1, 1938.

36. Becher, E.: Med. Klin. **34**:392, 1938.

to interference with the inferior vena cava. The consequent congestion of the veins of the kidney results in passage of serum albumin into the urine and acidosis. Administration of alkali will diminish lordotic albuminuria or stop it. Lordosis produced even in the supine position will cause albumin to pass into the urine in these patients. No damage to the kidneys even occurs as a consequence of recurring albuminuria. The condition is ameliorated by exercise, psychic treatment and military service.

[EDITORIAL NOTE.—One of the editors has followed a large group of children with this condition for a number of years. The albuminuria can be stopped when the lordosis, which frequently involves the lower dorsal part of the spine, is corrected. The response to treatment is prompt. If albuminuria continues after correction of lordosis, early nephritis will usually be found.]

Gas Gangrene.—The data obtained from vital statistics and from a survey of hospitals in the state of New York (exclusive of the city of New York) were studied by Bryant and Chapman.[37] They used the data for the years 1932 to 1936 inclusive. Two hundred and eight cases of gas gangrene were reported. One hundred and thirty-five of the patients were given an antitoxin for gas gangrene. Of 9 who received only a prophylactic dose of this serum, 2 died. Of 84 who received therapeutic doses, 29 died. Of 51 who received no serum, 35 died. These figures are not wholly correct, since a number of patients died from the disease which preceded the gas gangrene. The authors' statistics suggest that infection with the gas bacillus is as common as tetanus.

FRACTURES AND DISLOCATIONS

Treatment of Injuries of the Cervical Part of the Spine.—Forty-three patients with recent and old fracture-dislocations of the cervical part of the spine were treated by Crutchfield,[38] who uses a special instrument consisting of very small tongs for skeletal traction on the skull, held in place by a set screw. The tongs are applied through small stab wounds on either side, just large enough to admit the drill guard, which is drilled in for a distance of 3 mm. in children and 4 mm. in adults. The fixed guard prevents excessive penetration. The points of the tongs are fitted into the bone perforations and held in position until the tongs have been locked. Of the 43 patients treated, 14 died as the result of damage to the spinal cord and associated injuries. Twenty-nine cases, therefore, were analyzed for this report. The advantages of this method of treatment are numerous; headache and other disagreeable symptoms are

37. Bryant, T. L., and Chapman, O. D.: New York State J. Med. **38**:696, 1938.
38. Crutchfield, W. G.: J. Bone & Joint Surg. **20**:696, 1938.

eliminated, the care of the skin is much easier, and the patient is allowed more freedom of movement. The author has never used traction of more than 25 pounds (11.3 Kg.). In recent cases of injury to this portion of the spine, reduction has been accomplished usually within a few minutes. By the application of efficient, properly directed traction the danger of increasing deformity is eliminated. Reduction, immobilization in plaster and removal of the tongs, all within a few hours, are carried out on patients who are able to stand such treatment, but most of the author's patients were too ill for immediate immobilization. In most cases he applied traction at once and on the following morning made a roentgenologic examination. If reduction had been accomplished and there was little or no injury to the cord, immobilization in plaster was carried out at once. Patients with injured spinal cords were kept in light traction, 4 to 6 pounds (1.8 to 2.7 Kg.) being applied, until they passed the critical ten day period. The author uses traction of 25 pounds (11.3 Kg.) for dislocations in the middle third of the cervical spine; in the upper third only 10 to 15 pounds (4.5 to 6.8 Kg.) is necessary. Excellent illustrations accompany the next.

Injury to the Spinal Cord During Reduction of Fractures of the Vertebrae.—Of 70 patients with fracture and dislocation of the thoracic and lumbar vertebral bodies treated by Rogers [39] in the past nine years, only 2 showed fracture dislocations and 2 showed crush fractures involving the posterior wall of the centrum with backward displacement of the bone fragments. In none of these 4 cases was there any evidence of injury to the cord or pressure on the nerve roots immediately after the injury. In 3 cases paralysis developed as a result of treatment: in 2 cases of fracture dislocation during reduction and in 1 case of vertebral fracture two years after injury. In none of the other 66 cases, in which the usual wedge compression was present, was there slightest evidence of pressure on the spinal cord or the nerve roots incident to treatment. The author groups all fractures of the vertebral bodies, therefore, into two groups, the "safe" group, in which the fracture does not involve the posterior wall of the centrum (this represents 90 per cent) and the "dangerous" group, which includes all dislocations and all fractures involving the posterior wall of the centrum. It is essential, therefore, that the alinement of the articular processes be determined accurately before reduction is attempted. If there is lateral disalinement, the reduction should be open and flexion should be employed to disengage the locked processes. Extension of the spine in such a case may injure the cord or the nerve roots. Traction alone will not free locked articular processes.

39. Rogers, W. A.: J. Bone & Joint Surg. 20:689, 1938.

Postural Reduction of Fractures of the Spine.—Watson-Jones [40] feels that in reduction of fractures of the spine, hyperextension to the normal limit is necessary. This position varies considerably in different patients. Therefore he feels that controlled degrees of extension by slings or curved surfaces are imperfect. Instead the trunk should be entirely unsupported, so that it sags into space to the limit of the patient's movement in extension. The patient rests on two tables in such a way that his abdomen sags between the two. The legs and about three fourths of the thighs rest on the lower table and about two thirds of the upper parts of the arms remain on the upper table. The author feels that if more of the body is supported by the table than this the spine cannot sag sufficiently to give complete extension. He reports a series of 252 fractures of the spine and classifies them into three groups, namely, simple wedge fracture, comminuted fracture and fracture dislocation. The simple wedge fracture is the most common and is due to falling from a height and landing on the heels or the buttocks. Often the intervertebral disks are uninjured, and spontaneous ankylosis is rare. The comminuted fracture is the next most common and is caused by forcible acute angulation. The intervertebral disks are ruptured, and bony ankylosis is common. Fracture dislocation is due to the fall of a weight on the shoulders, and the spinal cord is usually injured. In the wedge and comminuted types of fracture excellent anatomic results are obtainable by the postural method of treatment. Eighty per cent of the patients resume their original occupation; the average period of disability is ten months. In cases of fracture dislocation, immobilization and extension are advisable. Laminectomy is not advisable. The prognosis is bad for high thoracic dislocations with paraplegia, fair for cervical injuries and good for lumbar injuries. The author lists common sources of failure as follows: Uncorrected wedging causes persistent pain due to interarticular joint strain. Neglect of finer details of the technic of postural reduction causes failure. The jacket must not be cut below the clavicle or above the groin; the cutting of an abdominal window is not advisable. Early manipulation is safe. The jacket must be renewed every two weeks. The patient must be immobilized for from four to six weeks. Posterior spinal splints are not advisable. Two hyperextension fractures are reported. One was a fracture of the vertebral body, and the other was a fracture of the pedicle. A fracture dislocation with locking of the articular processes can be treated only after one, and frequently both, articular processes have been excised.

40 Watson-Jones, R.: J. Bone & Joint Surg. 20:567, 1938.

Recurrent Dislocation of the Shoulder.—Bankhart[41] points out that ordinary dislocation of the shoulder and recurrent dislocation are entirely different injuries. The former is caused by a fall on the abducted arm, levering the head of the humerus out through the inferior part of the capsule, which heals readily after reduction. The latter injury is caused by a fall on the back of the shoulder or on an elbow directed backward, which forces the head of the humerus forward and shears off the fibrocartilaginous glenoid ligament from its attachment to the bone. There is no tendency for this ligament to reattach itself to the bone, so the defect is permanent. The author has exposed this lesion at operation in 27 consecutive cases of recurrent dislocation. The exposure is made by approaching between the deltoid and pectoralis major muscles. The coracoid process is divided by an osteotome and pulled downward. The tendon of the subscapularis muscle is exposed and divided, exposing the joint capsule. The periosteum is raised over the anterior aspect of the neck of the scapula, and the joint capsule is sutured to the bare bone thus exposed. In all the author's 27 cases full movement of the joint was recovered, and there was no recurrence of dislocation.

Excision of Ununited Scaphoid Bone.—Davidson and Horwitz[42] removed the carpal scaphoid bone from 8 patients in whom nonunion persisted after fracture; in 7 the excision of the scaphoid was complete, and in 1 it was partial. The end results in 5 instances were good, the patients returning to their former work. There was slight radial deviation in 2 instances. In 2 patients with nonunion of two years' duration the end result was good but there was considerable osteoarthritis. In 1 patient who had nonunion of seven years' duration there was much pain and osteoarthritis. The authors feel that excision should be done early when nonunion is present, before secondary arthritic changes have taken place.

Pseudarthrosis of the Tibia.—Hallock[43] states that in the past two methods of repair have been used chiefly in treatment of pseudarthrosis, namely, open reduction and massive graft. These measures, he states, have often been ineffective, especially in pseudarthroses of congenital origin and in children under 12. The author's technic consists in exposing the area of pseudarthrosis by subperiosteal dissection. The ends of bone are freshened or resected in sufficient amount to correct existing deformity and are placed end to end if possible. A broad, shallow longitudinal groove is fashioned in both fragments, extend-

41. Bankhart, A. S. B.: Brit. J. Surg. **26**:23, 1938.

42. Davidson, A. J., and Horwitz, M. T.: Ann. Surg. **108**:291, 1938.

43. Hallock, H.: J. Bone & Joint Surg. **20**:648, 1938.

ing from good bone in the upper fragment to good bone in the lower fragment. The groove is then filled with many small bone transplants or chips taken from the opposite tibia or from the ilium. The *periosteum is closed with interrupted sutures, and the procedure is* carried out under a tourniquet. Walking in the cast is usually allowed ten to twelve weeks after operation, at which time the cast is first changed. Immobilization in plaster is maintained until the roentgenogram shows sufficient new bone to permit function without support. The author feels that by this procedure adequate reparative growth of granulation tissue is promoted and that the ununited fragments are brought into extensive contact through the medium of many small bone masses which will quickly and readily become recalcified and rehabilitated. He has performed 7 primary and 4 secondary multiple bone transplant operations for 7 pseudarthroses. In 3 of the secondary operations a large graft was used in addition to the chips, chiefly for purposes of immobilization. Of the 7 primary operations, 4 succeeded and 3 failed. Excellent line drawings as well as roentgenograms illustrate the text.

Posterior Marginal Fractures of the Tibia.—D'Aubigne [44] offers a method of reduction of resistant trimalleolar fractures of the ankle. In these fractures it is usually the posterior marginal fracture of the tibia which is the chief obstacle to reduction. If the posterior marginal fracture involves a third of the articular surface the displacement is often irreducible; if it involves a half of the articular surface it is always irreducible, the posterior dislocation of the astragalus recurring as soon as the forward force is stopped. Open operation, which is commonly employed in the difficult cases, has several disadvantages. It may be impossible until very late because of excessive swelling and blisters. A large incision is necessary, with cutting of the achilles tendon. Accurate approximation of the posterior tibial fragment is difficult even by open operation. Lastly, the danger of infection is always present. The method of continuous traction by a pin in the os calcis is usually unsatisfactory, because reduction cannot be perfectly maintained. Consequently, the author has devised the following method: With the patient under general or spinal anesthesia, the leg is prepared with iodine and placed, with the knee flexed, on a Bohler reduction frame. Traction on the os calcis is established by a pin or a heavy wire, the force of the traction being obliquely upward and forward. A second pin is placed through the lower third of the tibia and is attached downward to the frame for counter-traction. By means of screwing up the traction on the os calcis, the fracture is reduced and

44. D'Aubigne, R. M.: J. de chir. **52**:168, 1938.

is checked by roentgenogram. In order to hold the reduction, a threaded steel pin is inserted, by means of a special three point guide, almost anteroposteriorly from the posterolateral border of the external malleolus, through the malleolus, to emerge through the tibia at its anteromedial part. Through small incisions, washers and nuts are placed on each end of the threaded pin, and the protruding ends of the pin are cut off and the wounds closed. The os calcis and tibial wires are then removed. A well molded plaster boot is applied, the foot being left free, and a walking iron is incorporated into the plaster. This technic has been used in 3 cases, with satisfactory results.

ORTHOPEDIC OPERATIONS

Operation for Paralysis of Intrinsic Muscles of Thumb.—Royle [45] describes an operation to restore the opposing function of the thumb when there is paralysis of the intrinsic thenar muscles. The flexor sublimis muscle to the ring finger is used. This muscle is divided just beyond its bifurcation at the base of the finger, drawn back and out at the wrist and then passed up the sheath of the long flexor of the thumb and attached one branch to the short flexor muscle and the other to the opponens pollicis. Reeducation is simple since attempting to flex the ring finger draws the thumb into opposition.

[EDITORIAL NOTE.—This operation seems simpler in technic than the other methods of tendon transplantation, most of which must utilize a tendinous pulley to secure pull in the correct direction.]

Spondylolisthesis.—Speed [46] describes a method of anterior fusion of the fifth lumbar vertebra to the sacrum by implantation of an autogenous bone graft through the body of the fifth lumbar vertebra, traversing its intervertebral disk into the upper sacral segment. This operation was performed for spondylolisthesis of the fifth lumbar vertebra. The patient was seen about six months after the operation. He was able to walk without support and complained of no pain in his back, though he still had some dragging sensation in the leg and tiring of the upper parts of the thighs after walking two blocks.

[EDITORIAL NOTE.—Most patients suffering from spondylolisthesis are relieved of their pain when a spinal support is properly fitted to the lower part of the back. In the opinion of the editors, so extensive an operative procedure as that just described is justifiable only when all conservative measures have failed.]

45. Royle, N. D.: Operation for Paralysis of the Intrinsic Muscles of the Thumb, J. A. M. A. **111**:612 (Aug. 13) 1938.
46. Speed, K.: Spondylolisthesis: Treatment by Interior Bone Graft, Arch. Surg. **37**:175 (Aug.) 1938.

Fusion in Charcot's Disease of the Knee.—A single case of successful fusion of Charcot's knee joint was reported by Soto-Hall [47] in the hope that the technic used might be of value in lowering the high percentage of failures following operation for this disease. The author believed that failure of arthrodesis in these knees was the result of curtailment of the blood supply and sclerosis of the bones. Consequently he performed the arthrodesis in two stages. First the knee joint was exposed and multiple ¼ inch (0.6 cm.) drill holes were made in both the femur and the tibia. Five weeks later the joint was again opened and a fusion operation was performed, the bones being fixed with two Steinman pins. Union was obtained, and the patient walked without support after seven months.

Resection of the Proximal Phalanx of the Great Toe for Hallux Valgus.—Lindemann and Meyerhoff [48] report a seven year follow-up on a series of 104 operations of a total of 128 performed for hallux valgus. The procedure in each instance was that popularized by Brandes in 1928 and consisted of resection of two thirds of the basal phalanx and lengthening of the shortened extensor hallucis muscle. Fifty-two patients were completely free from pain and presented a cosmetically satisfactory great toe. In 40 cases the results were termed functionally satisfactory. However, there appeared in various members of this group mild pain, recurrent deviation of the toe, shortening of the toe and limited articular motion. In 12 cases in which treatment failed there was either stiffening of the metacarpophalangeal joint or recurrence of the hallux valgus. Only 2 patients of this group complained of pain. As a rule, the patient is well three or four weeks after operation. Physical therapy and supports are employed in the after-care.

Treatment of Severe Paralytic Calcaneus.—Tendon transplants have been employed by Leveuf and Bertrand [49] in all cases of paralytic calcaneus in spite of the theoretic objection that the substituted muscles are very weak compared with the gastrocnemius muscle. The deformity must be reduced before the transplant is done, and only muscles which have the function of plantar flexion should be used. The bony correction must fulfil two conditions: 1. The relations of the calcaneus with the forefoot must be reestablished, and the arm of the calcaneal lever must be elongated so that the transplanted muscles will work at a mechanical advantage. 2. The articulations which permit lateral motion must be fused so as to assure lateral stability and to permit all muscles to act only as flexors and extensors. In most cases, the operation on the bones and the tendons has been done at the same time. The incision curves

47. Soto-Hall, R.: Ann. Surg. **108**:129, 1938.

48. Lindemann, K., and Meyerhoff, M.: Ztschr. f. Orthop. **67**:36, 1938.

49. Leveuf, J., and Bertrand, J.: J. de chir. **52**:145, 1938.

around the external malleolus to end on the dorsum of the foot. The peroneal tendons are isolated and cut as far distal as possible. The midtarsal and subastragalar joints are next resected. The head and neck of the astragalus are excised to allow backward displacement of the calcaneus. A wedge-shaped resection of the subastragalar joint is done with the base posteriorly, most of the wedge being taken from the calcaneus. This allows correction of the os calcis. In order to correct the cavus fully, a plantar fasciotomy may be done, but overcorrection should be avoided. After this resection it is noted that the scaphoid forms an anterior block. In the tendon transplant all the flexor muscles can be utilized, but as a rule both peroneals and the tibialis posterior are the ones most frequently used. The flexor hallucis and flexor digitorum longus muscles should not ordinarily be used, since they are important for a good gait. The peroneus brevis muscle alone should not be transplanted, since the longus muscle will then increase the cavus. In the operation the tendons are cut as far distally as possible and are then passed through osseous tunnels on the posterosuperior aspect of the calcaneus. Reefing of the achilles tendon is done only when there is some power left in the muscle. The foot is immobilized in plaster for two months. Walking is permitted in three months, with use of a device to raise the heel.

Recurring Deformity in Stabilization of the Foot.—A series of consecutive stabilizations of the foot for correction of the deformities associated with residual poliomyelitis has been studied by Crego and McCarroll [50] with reference to recurrent deformities. They found that such recurrences were caused by some form of abnormal muscular control. They decided that in order to prevent such secondary manifestations it is essential that the muscular power on the medial and lateral aspects of the ankle joint be perfectly balanced or completely removed after arthrodesis. Because of the difficulty encountered in estimating the exact power of individual muscles, the peroneal and the posterior and anterior tibial muscles are now transplanted to the midline posteriorly or anteriorly, unless the muscles are known to be completely paralyzed. If transplantation is not needed it is better to excise the tendons thoroughly. The only exception to this is in case of a cavus deformity secondary to paralysis of the intrinsic muscles of the foot in which all the long muscles are known to be normal in power. Other etiologic factors associated with malformation are tibial torsion, knock knee and exaggerated bow in the lower thirds of the legs. The authors feel that in stabilization of any foot the foot should be placed in correct alinement with the malleoli of the ankle joint without regard to other deformities. Procedures necessary for the correction of other deformi-

50. Crego, C. H., and McCarroll, H. R.: J. Bone & Joint Surg. **20**:609, 1938.

ties are carried out at a later operation in order to establish a satisfactory line of weight bearing in the extremity as a whole. Four of the authors' cases showed recurrence as a result of stabilization formed at too early an age. Recurrence could have been prevented, the authors feel, by waiting until the child was 8 years old before performing the operation. After deformities have once recurred, they are corrected by restabilization of the foot, followed by removal or correction of the cause of recurrence.

<div align="center">RESEARCH</div>

Chemical Composition of Voluntary Muscle.—Reinhold and Kingsley[51] studied the chemical composition of voluntary muscle obtained for biopsy from 12 patients suffering from muscular dystrophy and from 16 patients suffering from other muscular diseases. They found that the creatine concentration is lowered in the early stages of muscular dystrophy, before there is much muscular impairment. As the disease advances the creatine loss becomes greater. The total acid-soluble phosphorus content was also lowered in proportion. No change was observed in the results of chemical analysis after glycerin feeding for as long as twenty-two months. The histologic picture also remained the same. In myasthenia gravis there was a higher concentration of soluble ester phosphorus. In semistarvation the creatine content was lowered, as was the total acid-soluble phosphorus content. In myositis the changes were comparable to muscular dystrophy but were milder in degree. Less pronounced changes were observed in diseases of the nervous system. The authors state that chemical analysis of muscle is an aid in diagnosis and in estimating the degree of muscular deterioration.

Electrocoagulation of Osseous Tissues.—Zschau[52] reports on the electrocoagulation of bone, bone marrow, cartilage, periosteum and synovial membrane in guinea pigs. Bone is the most sensitive of these structures; cartilage is the least sensitive. When periosteum is destroyed by a strong coagulation current, it is replaced by fibrous tissue without osteoplastic power. Weak coagulation, on the other hand, excites bone formation. The synovial membrane was replaced by granulation tissue, which in a few weeks resembled the original synovial tissues.

Experimental Osteomyelitis in Rabbits.—Thompson and Dubos[53] in a study to test the virulence of various strains of Staphylococcus aureus found that they were able to produce osteomyelitis in rabbits. The virulence of the staphylococci was raised by their passage through the animal species. In further studies on 31 rabbits 2 months old 18 were found to have osseous lesions after intravenous injections of

51. Reinhold, J. G., and Kingsley, G. R.: J. Clin. Investigation **17**:377, 1938.
52. Zschau, H. D.: Ztschr. f. Chir. **250**:89, 1938.
53. Thompson, R. H. S., and Dubos, R. J.: J. Exper. Med. **68**:191, 1938.

staphylococci. Nine of the animals died from general infection in too short a period for the development of osseous lesions. Fifty-five lesions were observed in the bones of the 18 rabbits. Forty-seven of these lesions were at the ends of the long bones. Serous effusions into neighboring joints were commonly observed, but purulent arthritis occurred in only 8 instances. The microscopic appearance of the osseous lesions was similar to that of osteomyelitic lesions in man.

[EDITORIAL NOTE.—This interesting study suggests that blood-borne infection lodges much more frequently in bones than in joints. It offers a possible experimental approach to therapeutic endeavors which could eventually be applied to human osteomyelitis.]

Hereditary Bone Tumors in Mice.—Pybus and Miller [54] obtained 260 bone tumors, chiefly sarcomas, in mice from an inbred strain. These tumors developed in a cancer-producing strain of mice. The authors have been able to secure an incidence of 10 per cent of bone tumors. The most common sites of the lesions were the femur, the tibia and the spine. Histologically the authors were able to study tumors from the earliest proliferation of osteoblasts to all gradations of differentiation and malignancy. They feel that further study of this strain of mice may help in solving some of the problems presented by bone tumors in man.

Osseous Lesions in Experimental Scurvy.—Ham and Elliott [55] produced protracted moderate scurvy in young guinea pigs by feeding them diets containing less than adequate amounts of vitamin C. Longitudinal growth of bone continued in the peripheral part of the epiphysial plate and in the ring of diaphysis adjacent to the periphery of the plate. In the epiphysis a diminution in the amount of bone supporting the articular cartilage was found. The authors suggest that certain features of osteoarthritis may be the effect of a long-continued moderate deficiency of vitamin C.

54. Pybus, E. C., and Miller, E. W.: Brit. M. J. **1**:1300, 1938.
55. Ham, A. W., and Elliott, H. C.: Am. J. Path. **14**:323, 1938.

INDEX TO VOLUME 38